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American Heart Journal

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Original Communications

A BALLISTOCARDIOGRAPHIC STUDY OF 369 APPARENTLY NORMAL PERSONS

AN ANALYSIS OF "NORMAL" AND "BORDERLINE" BALLISTOCARDIOGRAMS

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SINCE THE publication of the classic paper of Starr and associates in 1939[1] ballistocardiography has received increasingly greater attention and, during the last few years, has been subjected to considerable clinical application. Initially Starr was interested in the high-frequency ballistocardiograph as a method for measuring cardiac output; he developed formulae for its calculation and set up normal standards for young men and women.[2] Since then the cardiac output formula has undergone several modifications, the most recent being that by Tanner[3] who set up new normal standards for stroke volume and cardiac output. On the basis of recent cadaver studies Starr and associates[4] believe that, while the relationship between cardiac output and the ballistocardiogram is a distant one, a much closer relationship exists between the maximum force produced during cardiac systole and the amplitude of the ballistocardiogram. Accordingly, normal standards were set up for "maximum cardiac force."

Aside from work relating to cardiac output there have been few quantitative studies on high-frequency ballistocardiograms. In a recent paper Starr and Hildreth[5] reported the means and limits for certain wave amplitude and duration measurements calculated from the ballistocardiograms of sixty-five subjects who had remained healthy over a period of ten to fourteen years. They suggested that the normality of measurements from a ballistocardiogram could be determined by comparing them with the limits defined for appropriate age groups and body

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sizes. Brown, Hoffman and deLalla[6] devised a useful classification system for the qualitative evaluation of abnormal ballistocardiograms but they made no attempt to set up rigid standards of normality for the ballistocardiogram. The lack of more precise criteria of normality has naturally made for inconsistency in interpretation, both from one observer to another and for the same observer from time to time. Undoubtedly, it will be extremely difficult to establish normal standards, not only because of the great complexity of the ballistocardiogram with its numerous variables but also because of the different methods employed in obtaining the records. However, it cannot be denied that this goal must be attained before interpretation can be placed on a sound basis. The first step would seem to be a detailed quantitative study of the ballistocardiograms from normal individuals with the purpose of defining the "average" ballistocardiogram, determining the limits of individual variation and seeking the causes of variability. This was one of the purposes for which the present study was designed.

Earlier reports by Starr[7,8] and more recent ones by a number of investigators[6,9-12] indicate that the ballistocardiogram is frequently abnormal in patients with coronary artery disease, many of whom have no other objective evidence of heart disease. These findings are all the more encouraging because of the difficulties so frequently encountered in establishing a diagnosis in this condition. However, to be of diagnostic value ballistocardiography should make possible the segregation of normal individuals from those with heart disease. In the absence of symptoms and signs of cardiovascular disease (or of conditions known to affect the heart and circulation) young persons almost invariably, if not always, have normal ballistocardiograms. As regards older persons Starr[13] obtained abnormal records from only four of ninety apparently normal subjects above the age of 40, an incidence of only 4.4 per cent. On the other hand Dock, Mandelbaum and Mandelbaum[9] (using the electromagnetic direct-body pickup) have published data on 100 normal subjects indicating a rapidly increasing incidence of abnormality in those above the age of 40. More recently Taymor and associates[12] (using the photoelectric direct-body pickup) found abnormal ballistocardiograms before or after exercise in 37.3 per cent of a group of subjects above the age of 50 who had negative Master "two-step" exercise tests.

In 1948 a long range investigative program was initiated in this laboratory for the study of patients with coronary artery disease. Shortly thereafter we became so impressed with the high frequency of abnormal ballistocardiograms in older normal subjects that a parallel long-term study was also set up for clinically normal persons. Our belief that this study was necessary for the evaluation of the diagnostic significance of ballistocardiography in coronary artery disease has been fully justified. The results to be reported here were obtained from the initial observations made on the individuals in this normal control group.

METHODS AND MATERIALS

1. *General.*

The normal control group consisted of 369 individuals, 261 men and 108 women, ranging in age from 20 to 84 years. The group was made up of medical

students, doctors, nurses, hospital employees, business men, housewives, and a few patients in whom there was no evidence of cardiovascular disease. Requirements for inclusion in this group were: (1) no symptoms or history of cardiac disease, (2) normal physical examination, (3) normal cardiac size by roentgenogram, and (4) normal blood pressure (not over 140/90 mm. Hg below age 50 and not over 160/100 mm. Hg above age 50).

Each subject had an electrocardiographic survey which included the standard limb leads, the unipolar limb leads and six unipolar precordial leads. All electrocardiograms were read by one of us, without knowledge of the subject's clinical state or interpretation of his ballistocardiogram, and the records were classified as normal, borderline or abnormal in accordance with generally accepted criteria.

Conventional head-foot ballistocardiograms were recorded on all subjects using a Starr-type high-frequency bed; most of the records were taken with the bed frequency at 9 cycles per second. The bed was calibrated loaded with 150 pounds dead weight so that 280 Gm. produced a deflection of 1 centimeter. Respiration (belt pneumograph) and the electrocardiogram (Lead II) were recorded simultaneously.

In most of the subjects ballistocardiographic "vector" records were taken by means of a turntable method previously described.[14] The 60° rt. record was taken with the turntable rotated counterclockwise (viewed from above) 60° away from the head-foot axis. The 90° rt. or lateral record was taken with the long axis of the body perpendicular to the long axis of the bed (with the right side of the body facing the foot of the bed) and represented the side-to-side movements of the body. Orientation of these records is usually the same as for the head-foot record, that is, the I and K waves are negative or downward and the H and J waves are positive or upward. The shape of the systolic complex in these two vector records is usually similar to that in the head-foot record.

Records were taken on most of the subjects before and during abdominal compression; a blood pressure cuff, fixed snugly in place over the midabdomen by means of a large abdominal binder, was inflated to 30 mm. Hg pressure and allowed to remain for three minutes after which time a ballistocardiogram was recorded.

All subjects were allowed to rest for at least ten minutes on the ballistocardiograph bed before records were taken; no attempt was made to secure records in the postabsorptive period only.

All of the ballistocardiograms were read by one of us and were classified qualitatively as normal, borderline, or abnormal. This system of classification was necessary because one of the purposes of the study was to analyze the ballistocardiograms quantitatively. Since some of the records were so altered in wave form that detailed measurements could not be made, it was necessary to separate them qualitatively from the remaining records and to classify them as abnormal. The remaining ballistocardiograms, which did lend themselves to quantitation, were qualitatively divided into normal and borderline categories on the basis of the wave form usually seen in healthy young adults. The records in these two groups were then separately measured and analyzed by methods to be described below. The final result was a quantitative multiple term definition of normal and

borderline ballistocardiograms as they were originally qualitatively classified. Had it been possible to analyze all of the records in a single group, without dividing them empirically into categories, the results, obviously, would have been far more meaningful. However, this was not possible and the procedure chosen is believed to be the most satisfactory compromise. By attempting to define what is meant by a normal ballistocardiogram, the results offer a crude guide for ballistocardiographic form evaluation until more precise standards of normality are evolved.

II. *Methods for Quantitative Analysis of Normal and Borderline Ballistocardiograms.*

Pulse rate was estimated by counting the number of beats in a twenty second interval (to the nearest 0.1 beat) and multiplying by 3. Three pairs of ballistic complexes, each pair consisting in a representative large one (inspiratory) and a representative small one (expiratory), were used for the measurements. Time intervals were measured to the nearest 0.01 second. The P-H interval was measured from the beginning of the P wave (electrocardiogram) to the peak of the H wave (ballistocardiogram); the remaining intervals were measured from the beginning of the electrocardiographic Q wave to the tips of the various ballistic waves (Q-H, Q-I, Q-J, and Q-K).

The upper edge of the ballistocardiographic tracing was used as the "line of no thickness" in all measurements allowing the width of the tracing (or string shadow) to be ignored. Base lines were drawn through all complexes to be measured. Durations of the I and J waves were measured in each complex and were averaged to give the mean duration for each wave (I_t and J_t) and for the two combined (IJ_t).

Amplitudes of the I, J, and K waves were measured to nearest 0.5 mm. in the three pairs of complexes, and these yielded inspiratory, expiratory and mean I, J, and K values; the mean amplitude of the I, J, and K waves (I_M, J_M and K_M) represent an average of the inspiratory and expiratory amplitudes. These measurements were used to define inspiratory, expiratory and mean IJ amplitudes (IJ_I, IJ_E and IJ_M) and mean JK amplitude (JK_M). Two amplitude ratios were derived: one expressed the relationship between mean JK and IJ amplitudes (JK_M/IJ_M) and the other expressed the relationship between the amplitudes of the H and J waves in expiratory complexes ($H_E/J_E \times 100$).

In calculating stroke volume the Starr area formula,[13] as modified by Tanner,[3] was used:

$$\text{S.V. (in cc.)} = \sqrt{(\text{Area } 2\,I + J)\sqrt{C}}$$

Stroke volume, cardiac output, and cardiac index were calculated.

Three different indexes were used for estimating the degree of respiratory variation in the ballistocardiogram:

1. One index (Respiratory Variation Index) is identical with Brown and associates'[6] Respiratory Variation Index except that Starr's newer area formula for calculating cardiac output was used instead of the older amplitude formula:

$$\text{Respiratory Variation Index} = \frac{\text{C.O. (Inspiratory)} - \text{C.O. (Expiratory)}}{\text{Surface Area}}$$

where Respiratory Variation Index is expressed in cc./M², C.O. in cc./Min. and surface area in square meters.

2. The second ("Rsv") is the ratio of expiratory and inspiratory stroke volumes:

$$\text{"Rsv" (in \%)} = \text{S.V.}_E/\text{S.V.}_I \times 100$$

3. The third ("Ra") is the ratio of expiratory and inspiratory IJ amplitudes:

$$\text{"Ra" (in \%)} = IJ_E/IJ_I \times 100$$

The effect of abdominal compression was determined by comparing amplitude and respiratory variation measurements from the records taken before and during abdominal compression (30 mm. Hg).

IJ amplitude was measured in the 60° rt. and 90° rt. (lateral) vector records and these amplitudes were related to IJ amplitude in the head-foot record, for example, IJ (Lat.) / IJ (H-F) × 100.

An effort was made to determine roughly the position of the heart within the chest in order to compare it with certain ballistocardiographic measurements. Lines representing the long axis of the heart and the vertical midline were drawn on chest roentgenograms (erect) and the acute angle produced by the intersection of these two lines was measured. In addition, the electrocardiographic QRS axis was used as a crude index of cardiac position.

A difference between two proportions or means is considered significant when the difference is over twice as great as the standard error of the difference, that is, d/S.E. > 2.0. The coefficient of variability is given by the ratio, standard deviation/mean × 100. A correlation coefficient (r) is considered significantly different from 0 when it is over twice as great as its standard error, that is, r/S.E. > 2.0. First order and partial correlations were computed by standard statistical techniques. The standard deviation of measurement about a regression equation is given by the formula:

$$\text{S.D.}_{y \cdot x} = \text{S.D.}_y \sqrt{1 - r^2(xy)}$$

It can be seen from this relationship that a value of r less than 0.4 will yield only a very small reduction in scatter. Therefore although an r of less than 0.4 may be significantly different from zero it represents a small degree of correlation.

RESULTS

I. *General.*

The ballistocardiographic and electrocardiographic findings by age decade and by sex are summarized in Table I. Figure 1 shows the frequency of normal, borderline and abnormal electrocardiograms and ballistocardiograms for each decade. There were no abnormal electrocardiograms in individuals under the age of 40; in the fifth decade 2.6 per cent were abnormal and the incidence rose gradually to a maximum of 8.3 per cent in the eighth decade. There were no abnormal ballistocardiograms in individuals under the age of 40 but thereafter the incidence of abnormal records rose precipitously to a maximum of 91.7 per cent in the eighth decade. There were statistically significant differences in the frequency of abnormal ballistocardiograms in successive decades from the fourth through the eighth.

TABLE I.

		AGE GROUP																											
		20-29				30-39				40-49				50-59				60-69				70-79				80-89				TOTALS			
		BCG		ECG		BCG		ECG		BCG		ECG		BCG		ECG		BCG		ECG		BCG		ECG		BCG		ECG		BCG		ECG	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Men	N*	44	100	44	100	49	98	50	100	38	67.8	50	89.3	21	41.2	42	82.3	13	24.1	41	75.9	0	0	3	75	1	50	2	100	166	63.6	232	89.9
	B*	0	0	0	0	1	2	0	0	11	19.7	4	7.1	11	21.6	6	11.8	6	11.8	10	18.5	0	0	0	0	0	0	0	0	29	11.1	20	7.7
	A*	0	0	0	0	0	0	0	0	7	12.5	2	3.6	19	37.2	3	5.9	35	64.8	3	5.6	4	100	1	25	1	50	0	0	66	25.3	9	3.4
Women	N	25	100	25	100	18	100	18	100	20	95.2	19	90.5	11	68.8	16	100	3	16.7	16	89.0	0	0	5	62.5	0	0	2	100	77	71.3	101	93.5
	B	0	0	0	0	0	0	0	0	0	0	2	9.5	1	6.3	0	0	2	11.0	1	5.5	1	12.5	3	37.5	0	0	0	0	4	3.7	6	5.6
	A	0	0	0	0	0	0	0	0	1	4.8	0	0	4	24.9	0	0	13	72.3	1	5.5	7	87.5	0	0	2	100	0	0	27	25.0	1	0.9
Combined	N	69	100	69	100	67	98.5	68	100	58	75.4	69	89.6	32	47.8	58	86.7	16	22.2	57	79.2	0	0	8	66.6	1	25	4	100	243	65.8	333	90.3
	B	0	0	0	0	1	1.5	0	0	11	13.0	6	7.8	12	17.9	6	8.8	8	11.1	11	15.2	1	8.3	3	25.1	0	0	0	0	33	8.9	26	7.0
	A	0	0	0	0	0	0	0	0	8	10.4	2	2.6	23	34.3	3	4.5	48	66.7	4	5.6	11	91.7	1	8.3	3	75	0	0	93	25.3	10	2.7
Totals																																	
Men		44				50				56				51				54				4				2				261			
Women		25				18				21				16				18				8				2				108			
Combined		69				68				77				67				72				12				4				369			

*N = normal, B = borderline, A = abnormal.

In the entire group of 369 individuals the ballistocardiograms were normal in 55.8 per cent, borderline in 9.0 per cent and abnormal in 25.2 per cent; the corresponding figures for electrocardiograms were 90.5 per cent, 6.8 per cent and 2.7 per cent. Of the ten subjects who had abnormal electrocardiograms, the ballistocardiogram was abnormal in nine; one person had a normal ballistocardiogram in the presence of right bundle branch block known to have been present for many years. Of the ninety-three subjects who had abnormal ballistocardiograms the electrocardiogram was abnormal in only nine (9.7 per cent) and was normal in 65 (69.8 per cent).

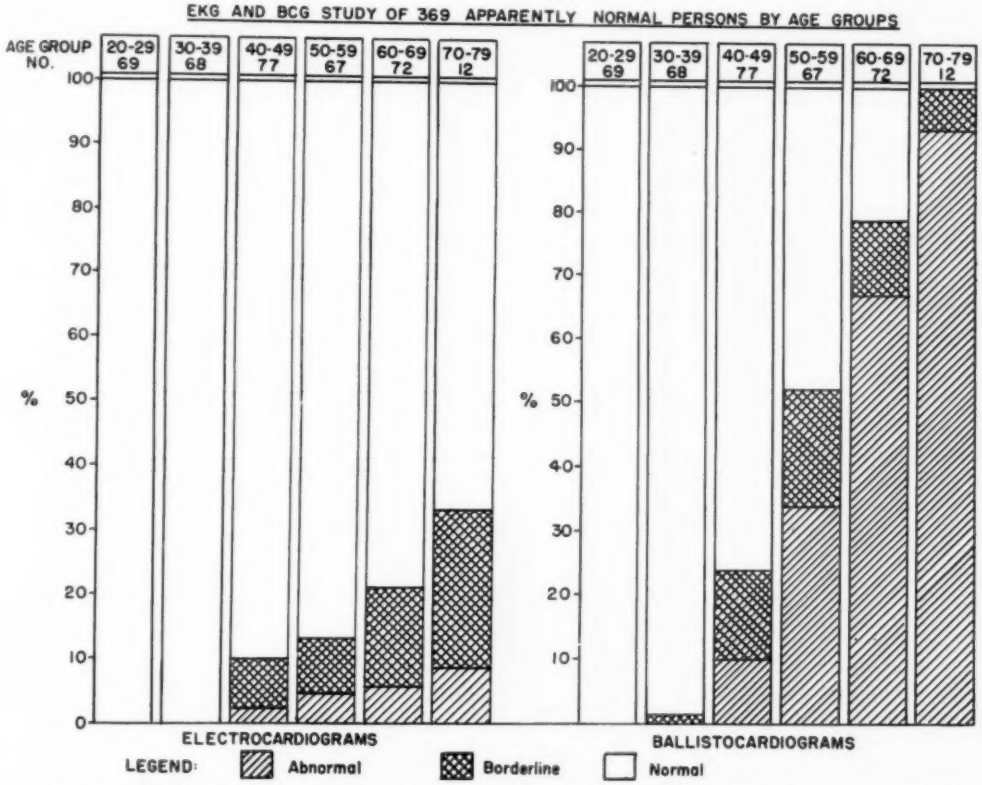


Fig. 1.—Results of electrocardiographic and ballistocardiographic study of apparently normal persons. The number of subjects in each age-decade is indicated just beneath the age group designation. The series includes 261 men and 108 women. Above the age of 40 the frequency of abnormal electrocardiograms increases gradually to a maximum of 8 per cent: abnormal ballistocardiograms increase precipitously to a maximum of 92 per cent.

II. *Results of Quantitative Analysis of Normal Ballistocardiograms.*

There were 243 ballistocardiograms classified as normal among the total of 369 records. There were no normal records in the eighth decade and only one in the ninth; this latter record was not included in the analysis which was carried out by age groups. The rapidly decreasing incidence of normal records above the age of 50 reduced the significance of the mean values in the sixth and seventh decades and produced an unintentional selection of the subjects in these two age groups. Although there were 155 subjects above the age of 50, only the 49 records classified as normal could be analyzed. The age distribution of men and women is similar.

A. Time Intervals.—Q-H, Q-I, Q-J and Q-K Intervals. There is no apparent age trend for any of these intervals. The Q-H and Q-I intervals are not significantly shorter for women than for men. However, the Q-J and Q-K intervals are slightly but significantly shorter in women; this difference may be related to body size. In men there is a significant positive correlation be-

tween Q-K and height ($r = +0.41$, r/S.E. = 4.7) and a more highly significant one between Q-K and weight ($r = +0.54$, r/S.E. = 6.3). Neither of these correlations is significant in women. In men there is a small but significant negative correlation between Q-K and pulse rate ($r = -0.28$, r/S.E. = 3.4) but this is not significant in women. In either sex different body weights and pulse rates have rather small effects on the Q-K interval, which is remarkably constant as indicated by a coefficient of variability of only 6 per cent for the entire series.

P-H, Q-H and P-R Intervals: The P-H interval shows a surprisingly small degree of variability (7 per cent for the whole series), smaller than that for the P-R and Q-H intervals. The mean P-H interval for 225 subjects of both sexes and all ages is 0.271 second (± .02). This interval increases slightly with age and is slightly longer in men than women.

The Q-H interval serves to establish the position of the H wave in time. If the Q-H interval is correlated with the electrocardiographic P-R interval a highly significant negative correlation results; this indicates that with a long P-R interval the H wave appears early (referred to the Q wave) and with a short P-R interval the H wave appears late.* This temporal relationship of the P and H waves explains the relative constancy of the P-H interval.

At least four factors appear to influence the duration of the I and J waves (IJ_t); they are pulse rate, body size (height, weight, or surface area), age, and sex. There is a small but significant negative correlation between pulse rate and IJ_t in men but none in women. Body weight and surface area show significant positive correlations with IJ_t in both sexes. Large individuals tend to have "broad" ballistic complexes.

IJ_t decreases slightly with age, being significantly shorter in subjects 50 to 69 years of age than in those 20 to 39. Both I_t and IJ_t are significantly shorter in women than in men and these differences are doubtless due to the differing surface areas of the two sexes. If the mean surface area for women is inserted in the regression equation for men, the predicted IJ_t is almost identical to the observed mean IJ_t in women.

Although age, pulse rate, and body size are significantly related to IJ_t, their influences are, nevertheless, small. Only when the individual effects are additive can remarkable departures of IJ_t be expected.

Comment: The definite relationship found to exist between the Q-H and P-R intervals logically suggests a relationship between auricular contraction and the ballistic H wave and supports the contention, first made by Nickerson,[15] that the H wave is due (in whole or in part) to auricular activity. This study yielded no data relating to the possible role of the apex thrust in the production of the H wave.

In spite of the rather large errors involved in measuring the duration of the I and J waves there were surprisingly high correlations between this variable and age, body size, and pulse rate. Duration of the I and J waves (IJ_t) decreases with increasing age and pulse rate but increases with increasing body size. One can only conjecture on the reasons for these relationships. The effect of age on IJ_t may be related to changes in the elasticity of the aorta; in older individuals the inelastic and sclerotic aorta acts as a rigid-walled tube. Increased rigidity of the aortic walls results in a greater pulse wave velocity so that the blood in the abdominal aorta and iliac arteries begins to accelerate sooner than usual after the onset of cardiac ejection. Since it is the impact of this blood column flowing into the zone of increased resistance at the bifurcation of the aorta which terminates the headward motion of the body (the J wave), an earlier impact might be ex-

*If the range of the P-R intervals is extended by the inclusion of records from other sources, the relationship between the electrical P wave and the ballistic H wave is more clearly demonstrable; with a P-R interval of 0.10 second the predicted Q-H is 0.15 second and with a P-R of 0.23 the predicted Q-H is 0.06 second.

pected to produce earlier cancellation of the J wave and consequently a shorter IJ duration. Hypertension should produce the same result inasmuch as pulse wave velocity tends to vary directly with intravascular pressure. Jones and Goulder,[16] using the low-frequency ballistocardiograph, found that the interval between the I and J peaks was significantly shorter in a group of hypertensive patients than in a group of normal subjects. The shortening of the IJ duration with increased pulse rates noted in this study may be explicable on the same basis inasmuch as diastolic pressure tends to be higher with fast pulse rates than with slow ones; it is probable that other factors such as ejection velocity are also concerned.

Body size also bears a relationship to IJ_t; this may be due to the fact that large persons tend to have long aortae. With a longer aorta the pulse wave must traverse a greater distance before it reaches the aortic bifurcation and hence the cancellation of the J wave is delayed. Against this explanation are the higher correlations of IJ_t with both surface area and weight than with height, which should be more closely related to aortic length than the other two. This same relationship was found to exist when the Q-K interval was correlated with height and weight. It is clear, in any case, that the "spread" of the systolic complex is related to body size, as Brown's and de Lalla's results indicated.[17] Although the duration of the systolic complex in the ballistocardiogram appears to be related to the individual's age, size, pulse rate, and possibly blood pressure, the duration measurements show little scatter and are restricted to rather small ranges.

B. *Amplitude Measurements.*—In Table II are summarized the amplitude measurements for the I, J and K waves by age decades for both sexes. The mean amplitudes for these three waves are significantly smaller in women than in men and all of them show progressive decreases with age. The absolute decrease in amplitude of the I and J waves is less striking in women than in men. The mean amplitudes of the I and J waves are significantly smaller in the combined 50 to 69-year group than in the 20 to 39-year group, in both sexes.

As one would expect from the preceding, IJ amplitude (inspiratory, expiratory, and mean) is significantly smaller in women than in men and is smaller in older than in younger subjects. IJ_M decreases about 2 mm. per decade in men and about 1 mm. per decade in women. At age 60, IJ_M in men is approximately 63 per cent of that at age 20; in women this value is 72 per cent. Therefore, the rate of decrease in IJ amplitude with age is both absolutely and relatively greater in men than in women.

It has been assumed that the differences in IJ amplitude between the two sexes are largely due to differences in body size. IJ_M in men is 49 per cent greater than that in women. When IJ_M is divided by surface area and the two sexes compared the men's values are still 26 per cent greater. Since such ratio methods have been objected to,[3] use was made of the regression, IJ_M on surface area. When the mean surface area of the women is inserted into the regression equation for men, the predicted IJ amplitude is 39 per cent greater than that actually observed in women. Thus, it would appear that differences in body size do not account for sex differences in IJ amplitude.

Furthermore, if IJ amplitude is related to body size one would expect the rather large scatter about the means (expressed by the coefficient of variability) to be reduced by correction for surface area. However, correction for body size did not reduce the scatter in either sex. In view of these findings it seemed advisable to study in detail some of the factors influencing ballistic amplitude.

Influence of Various Factors on Mean IJ Amplitude: The influences of age, sex, pulse rate, surface area, height, and weight on IJ_M were analyzed. Table III*A* shows the correlations relating these various factors. It is apparent that none of the variables except age show any important correlation with IJ_M. In order to assess the influence of each variable separately, partial correlations were calculated for the numerically large group of men. The results shown in Table

TABLE II. AMPLITUDE MEASUREMENTS

	AGE GROUP	NO.	AMPLITUDES										RATIO JK_M/IJ_M	
			MEAN I		MEAN J		MEAN K		INSPIRATORY IJ		EXPIRATORY IJ		MEAN IJ			
			MEAN, IN MM.	S.D.	MEAN, IN MM.	S.D.	MEAN, IN MM.	S.D.	MEAN, IN MM.	S.D.	MEAN, IN MM.	S.D.	MEAN, IN MM.	S.D.	MEAN	S.D.
Men	20–29	44	8.0	(2.5)	13.9	(3.0)	8.8	(2.6)	25.2	(5.1)	17.9	(4.4)	21.9	(4.5)	1.03	(.076)
	30–39	49	7.6	(2.0)	12.7	(3.1)	8.2	(2.3)	23.6	(6.2)	16.5	(4.2)	20.2	(4.9)	1.03	(.090)
	40–49	38	5.9	(1.6)	10.4	(2.4)	7.5	(2.0)	19.8	(4.9)	12.5	(3.3)	16.2	(3.7)	1.10	(.098)
	50–59	21	5.6	(2.1)	9.8	(2.7)	7.8	(2.8)	19.1	(5.6)	11.6	(3.9)	15.4	(4.6)	1.14	(.129)
	60–69	13	5.8	(1.9)	9.9	(2.7)	7.7	(2.3)	19.3	(4.5)	11.2	(3.4)	15.6	(4.3)	1.13	(.090)
	20–69	165	6.9	(2.1)	11.9	(3.3)	8.1	(2.4)	22.3	(6.0)	14.9	(4.8)	18.8	(5.2)	1.07	(.102)
Women	20–29	25	4.7	(1.1)	9.1	(2.6)	5.1	(1.5)	15.5	(2.7)	11.9	(2.0)	13.8	(2.2)	1.02	(.097)
	30–39	18	4.2	(1.0)	8.7	(1.4)	4.5	(0.8)	15.3	(2.9)	10.4	(2.1)	12.9	(2.1)	1.03	(.058)
	40–49	20	4.3	(1.0)	8.4	(1.8)	4.4	(1.7)	15.1	(3.1)	10.1	(2.7)	12.7	(2.6)	1.01	(.091)
	50–59	11	2.9	(0.8)	6.5	(1.2)	3.7	(0.8)	11.4	(2.1)	6.5	(1.8)	9.5	(1.8)	1.09	(.110)
	60–69	3	3.2	(0.9)	7.7	(2.3)	4.2	(0.7)	12.5	(3.2)	9.3	(3.3)	10.9	(3.3)	1.11	(.031)
	20–69	77	4.2*	(1.2)	8.4*	(1.8)	4.5*	(1.4)	14.7*	(3.1)	10.3*	(2.7)	12.6*	(2.7)	1.03*	(.098)
Men and Women	20–69	242	6.0	(2.2)	10.8	(3.3)	7.0	(2.7)	19.9	(6.3)	13.5	(4.7)	16.8	(5.4)	1.05	(.103)

*Signifies that the mean for women is significantly different from that of men.

TABLE III*A*.—FIRST ORDER CORRELATIONS

		MEN, 20-69 YEARS (165)					WOMEN, 20-69 YEARS (77)				
		AGE (YEARS)	PULSE RATE	SURFACE AREA (M^2)	HEIGHT (IN.)	WEIGHT (LBS.)	AGE (YEARS)	PULSE RATE	SURFACE AREA (M^2)	HEIGHT (IN.)	WEIGHT (LBS.)
P.R.	r =	−.002	—	—	—	—	−.167	—	—	—	—
	r/S.E.* =	0.03					1.5				
S.A.	r =	−.011	−.285	—	—	—	−.058	+.125	—	—	—
	r/S.E. =	0.13	3.6				0.5	1.1			
Wt.	r =	+.019	−.265	—	—	—	+.055	+.078	—	—	—
	r/S.E. =	0.2	3.4				0.5	0.7			
IJ_M	r =	−.484	−.130	+.123	+.129	+.056	−.437	+.084	+.205	+.166	+.176
	r/S.E. =	6.2	1.7	1.6	1.7	0.7	3.8	0.7	1.8	1.5	1.5
Area 2I+J	r =	−.473	−.199	+.208	—	+.156	−.486	+.012	+.321	—	+.294
	r/S.E. =	6.1	2.6	2.7		2.0	4.2	0.1	2.8		2.6
S.V.	r =	−.490	−.466	+.274	—	+.205	−.447	−.187	+.332	—	+.288
	r/S.E. =	6.3	6.0	3.5		2.6	3.9	1.6	2.9		2.5
C.O.	r =	−.481	+.380	+.046	—	—	−.484	+.639	+.334	—	—
	r/S.E. =	6.2	4.9	0.6			4.2	5.6	2.9		

TABLE III*B*. PARTIAL CORRELATIONS AND REGRESSIONS, IJ_M, MEN 20-69 YEARS

	CORREL. COEF. (r)	S.E.	r/S.E.*	REGRESSION COEF.**
IJ_M on Age (S.A. and P.R. Constant)	−.489	.079	6.2	−.2144 mm./year
IJ_M on S.A. (Age and P.R. Constant)	+.098	.079	1.2	+3.42 mm./M^2
IJ_M on P.R. (Age and S.A. Constant)	−.134	.079	1.7	−.0762 mm./beat

*A correlation coefficient (r) is considered "significant" when it is twice as large as its standard error, that is, r/S.E.>2.0.
**Regression coefficient expresses rate of change of IJ_M for unit changes in age, surface area, and pulse rate.

IIIB indicate that surface area and pulse rate have little influence on IJ amplitude leaving age as its principal determinant among the factors analyzed. Therefore in the regression equation pulse rate and surface area are not included. Fig. 2 shows the regression lines for men and women calculated from this equation.

It should be pointed out that the factors analyzed here account for only a part of the variability in IJ amplitude; other factors are responsible for the majority of the variation. No reasons were found to explain the differences between the two sexes.

The ratio JK_M/IJ_M progressively increases with age. This is due, not to an increase in JK_M with age (for it decreases), but rather to a relatively greater decrease in IJ_M with age. The ratio H_E/J_E was chosen for study because Starr's "early M" form (relatively tall H and short J) is a common early abnormality and usually appears first during expiration. The decade means show a progressive increase in the ratio with age; in the sixth decade the mean ratio is about twice as great as that in the third decade. This is due to the decrease in J amplitude with age inasmuch as there is little tendency for H to increase with age.

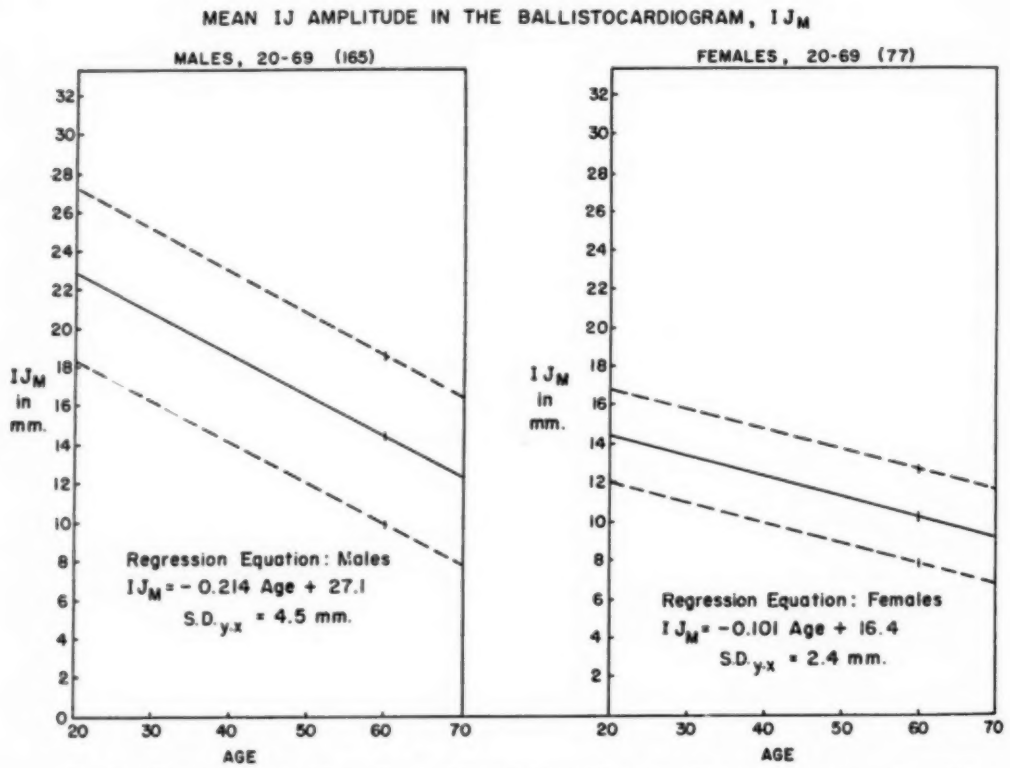


Fig. 2.—Changes in mean IJ amplitude of the ballistocardiogram with age. The intersection of the solid (regression) line with a vertical age line indicates the predicted value for mean IJ amplitude (IJ_M) at that age. The broken lines indicate the limits of one standard deviation (or standard error of estimate) layed off on either side of the regression line; 16 per cent of normal subjects fall below the lower broken lines. In men 60 years of age the IJ amplitude of the ballistocardiogram is only 63 per cent of that at 20; this value in women is 72 per cent.

Comment: The results indicate that there are progressive and significant decreases in the mean amplitude of the I and J waves and in their combined amplitude (IJ_M) in both sexes as age increases. The K wave decreases only slightly so that the ratio JK/IJ, increases with age. The IJ amplitude of the expiratory complexes decreases more rapidly than does that of the inspiratory or

mean complexes. The ratio of the amplitudes of the expiratory H and J waves (H_E/J_E) increases with age.

Statistical analysis of the amplitude data revealed good correlation between mean IJ amplitude and age but surprisingly little correlation between mean IJ amplitude and pulse rate or body size when the two sexes were treated separately. Correction of IJ_M for body size did not reduce scatter and the regressions indicated that surface area has only a minor influence on IJ_M. This lack of correlation is surprising since it has become rather generally accepted that ballistic IJ amplitude is related to body size. As a result of their changing concepts about the significance of the ballistocardiogram and its relationship to the force of cardiac contraction, Starr and associates[4] set up normal standards for IJ amplitude in the belief that this measurement is closely related to strength of the heart. Their standards were based on the measurements from a group of 100 subjects from 20 to 39-years of age about equally divided between the two sexes. IJ amplitude was correlated with surface area and regressions equations relating the two were set up for the whole mixed group; knowing the surface area one could predict the IJ amplitude and compare it with the observed value. Combining the data of men and women in this manner raises an objection from the statistical point of view for, if the correlation coefficient is to have meaning, both variables should be normally distributed; this should not be the case when the men and women are combined inasmuch as the means of both variables (IJ_M and surface area) are usually significantly different in the two sexes. In our normal group there was no significant correlation between IJ_M and surface area in either the men alone or the women alone, but there was a significant degree of correlation ($r = +0.45$, $r/S.E. = 6.9$) in the combined men-women group. Since it seemed probable that the significant correlation between IJ_M and surface area in Starr's normal group was a result of combining the two sexes, separate correlations for men and women were calculated from the data, kindly supplied to us by Dr. Starr, which were used in computing his regression equations. The results were very similar to those from our normal group; there was no significant correlation for either of the two sexes alone but there was a significant correlation ($r = +.44$, $r/S.E. = 4.5$) when the two sexes were combined. Thus it appears that the use of regressions based on groups containing both sexes can lead to large errors in the prediction of IJ amplitude from surface area and since there is no significant relationship between the two variables, IJ amplitude need not be corrected for body size.

The highly significant trend of IJ amplitude with age brings up a question regarding normal standards which has been posed by Starr on several occasions, namely: should an older person be judged by standards based on his own age group or by those based on a young age group? Follow-up studies by Starr[5,13] and others[10] will probably produce the best answer to this question. Until such an answer is forthcoming we are inclined to judge a man's performance by that of his contemporaries and it is for this purpose that the regressions in Fig. 2 were designed. However, the graph may be used regardless of whether an individual is referred to a younger age group or to his own.

There are two reservations regarding the use of these IJ amplitude regressions. Their validity above the age of 60 is questionable because of the small number of subjects in the older age groups with normal records. Secondly, there

TABLE IV. CARDIAC OUTPUT AND RELATED MEASUREMENTS

	AGE GROUP	NO.	PULSE RATE		AREA $2I + J$		STROKE VOLUME		CARDIAC OUTPUT		CARDIAC INDEX	
			MEAN	S.D.	MEAN (MM-SEC)	S.D.	MEAN (CC.)	S.D.	MEAN (L.)	S.D.	MEAN ($L./M^2$)	S.D.
Men	20–29	44	70.1	(9.4)	1.202	(.0286)	105.9	(13.5)	7.34	(.843)	3.87	(.54)
	30–39	49	70.1	(8.8)	1.124	(.3055)	101.2	(13.8)	7.04	(1.088)	3.56	(.59)
	40–49	38	70.3	(9.1)	0.859	(.2055)	88.6	(10.6)	6.18	(.880)	3.23	(.50)
	50–59	21	68.5	(8.7)	0.844	(.2670)	88.5	(14.7)	5.90	(1.007)	2.99	(.55)
	60–69	13	71.0	(10.6)	0.828	(.2670)	86.5	(14.8)	6.05	(.920)	3.26	(.52)
	20–69	165	70.0	(9.1)	1.025	(.3160)	96.7	(15.6)	6.70	(1.111)	3.48	(.59)
Women	20–29	25	74.3	(10.7)	0.737	(.1510)	81.1	(9.5)	6.00	(.935)	3.67	(.57)
	30–39	18	70.3	(7.8)	0.663	(.1120)	78.2	(6.9)	5.49	(.718)	3.38	(.42)
	40–49	20	71.7	(8.9)	0.661	(.1233)	77.8	(9.3)	5.52	(.725)	3.33	(.44)
	50–59	11	68.6	(7.8)	0.466	(.0822)	65.9	(6.8)	4.50	(.457)	2.81	(.29)
	60–69	3	70.2	(7.4)	0.503	(.1690)	67.7	(12.4)	4.69	(.603)	2.93	(.37)
	20–69	77	71.7	(9.2)	0.652*	(.1623)	76.8*	(10.1)	5.49*	(.919)	3.36	(.53)
Men and Women	20–69	242	70.6	(9.2)	0.905	(.3265)	90.4	(16.8)	6.31	(1.192)	3.44	(.58)

*Signifies that the mean for women is significantly different from that of men.

are not sufficient data available to allow a comparison of absolute amplitude measurements from records taken with different ballistocardiograph beds. There is reason to believe that there may be appreciable differences in absolute values from different beds even though static calibration is the same. Our IJ_M values are 20 to 30 per cent higher than Starr's for comparable age and sex groups.[4,5] Therefore, until calibration differences are clarified, it is suggested that each laboratory determine the mean IJ_M value for one age decade group in both sexes; a correction factor may be used to bring this mean value into line with our regression line for that age and sex group. The regression line and the limits will then apply to the measurements made from records taken with that particular bed on individuals over the whole age group.

C. *Cardiac Output Measurements.*—Table IV summarizes some of the measurements related to the calculation of cardiac output. Area 2I + J, stroke volume, and cardiac output all show progressive and significant decreases with age in both sexes and are all significantly greater in men than in women.

The correlation coefficients relating age, pulse rate, surface area and weight to area 2I + J, stroke volume, and cardiac output are given in Table III*A*. It may be seen that surface area correlates much better with area 2I + J and stroke volume than it does with IJ_M; this is due to the fact that both of the former include an IJ duration factor which correlates significantly with surface area. There is no correlation between cardiac output and surface area in men. The explanation for this peculiarity is to be found in the significant negative correlation between surface area and pulse rate; big men, who would tend to have high cardiac outputs, have lower pulse rates, which tend to produce low cardiac outputs. In women there is a significant correlation between cardiac output and surface area.

Comment: The results of the statistical treatment of the measurements relating to cardiac output are, in general, similar to those reported by Tanner.[3] For this reason multiple regression equations for stroke volume and cardiac output have not been set up. Our cardiac output figures are, on the average, about 17 per cent higher than the values predicted from Tanner's regression equation. This is to be expected, since Tanner's standards were based on records taken on Starr's ballistocardiograph which gives absolute amplitude values somewhat lower than ours.

D. *Respiratory Variation Measurements.*—All three indexes (R.V.I., "Ra," and "Rsv") show trends indicative of increasing respiratory variation with age. When the 20 to 39-year men's group is compared with the 50 to 69-year group, there are significant differences with all three indexes. The difference is most significant for "Ra," least for R.V.I. and intermediate for "Rsv." Comparison of similar groups of women yields a significant difference for "Ra" but not for the other two. "Ra" most clearly shows the difference between the young and older groups with respect to respiratory variation. The three indexes are also considerably different as regards variability. The coefficient of variability for R.V.I. is quite high, 48 per cent for the whole series, in contrast to the values for "Ra" and "Rsv" which are 16.7 per cent and 9.9 per cent, respectively. The value for "Rsv" is smaller than that for "Ra" because scatter is reduced when the square root is extracted in the stroke volume calculation. "Ra," the ratio of inspiratory and expiratory IJ amplitude, proved to be the simplest and most satisfactory of the three indexes of respiratory variation in the ballistocardiogram. Fig. 3 shows the regression equations and regression lines for "Ra."

Comment: Brown and associates[6,17] called attention to the increased respiratory variation in the ballistocardiograms of patients with angina pectoris and devised a method for expressing its magnitude. Using their ballistocardio-

graphic "Respiratory Variation Index" (R.V.I.) they found that forty-nine of fifty adults gave values which fell below 450 c.c. per square meter surface area whereas all of twenty-one patients with angina pectoris yielded values above this figure; their normal adults ranged in age from 20 to 70 but the bulk were between 25 and 35 years of age. These findings are of considerable importance but there are certain objections to the Respiratory Variation Index as it now exists. It was used in their Grade 1 and 2 abnormal ballistocardiograms and it would seem difficult to calculate cardiac output from records with these grades of abnormality

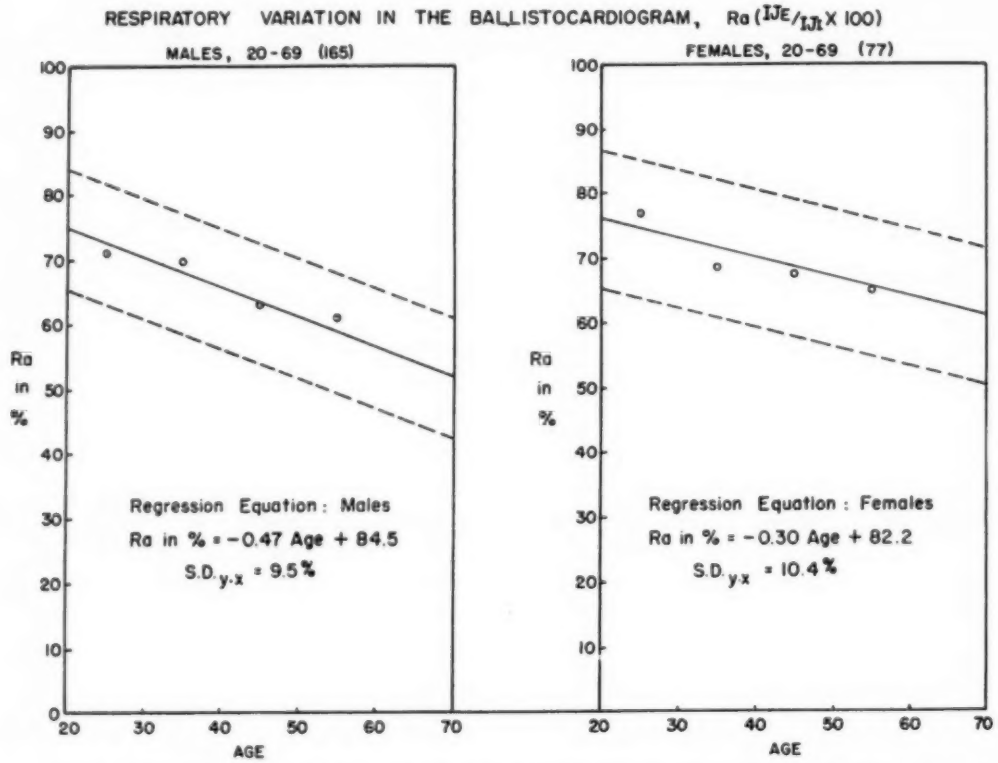


Fig. 3.—The effect of age on the respiratory variation in the amplitude of the ballistocardiogram. "Ra" is the ratio of expiratory to inspiratory IJ amplitudes expressed in percentage. An increase in respiratory variation is represented by a decrease in the value of "Ra." The decrease of "Ra" with age is significant in both sexes. The intersection of the slanting solid (regression) line with a vertical age line gives the predicted "Ra" value for that age. The broken lines are the limits of one standard deviation ($S.D._{x\,.\,y}$) about the regression line. The open circles represent the age-decade means.

(Brown and associates,[6] Figs. 4 and 5), especially the Grade 2 record in which half or more of the complexes are abnormal in form. Furthermore, since the absolute level of cardiac output is not corrected for, this index can be expected to vary directly with cardiac output, that is, R.V.I. will tend to be high when output is high and low when output is low. This is partially compensated for by the surface area factor, but there still remains the variability of cardiac index. The variability of the R.V.I., therefore, includes the variability of cardiac index as well as that of respiratory variation. This combination is probably responsible for the

unusually high coefficient of variability (48.2 per cent for the whole group) for the R.V.I. noted in this study. Our absolute R.V.I. values are considerably higher than Brown's; this difference can be attributed, at least in part, to the different formulae used in calculating cardiac output inasmuch as the more recent formula yields higher values than the older one used by Brown. It is also likely that our absolute amplitude values are larger than Brown's but this would have no effect on correlations or relative variability.

The other two indexes, "Rsv" and "Ra," are unaffected by absolute cardiac output and are far less variable than the R.V.I. Of the three, the ratio of expiratory to inspiratory IJ amplitudes ("Ra") is the easiest to calculate and can be applied to ballistocardiograms from which cardiac output cannot be calculated because of minor or moderate degrees of form abnormality.

It seems likely, as Brown and his associates suggest, that an increase in respiratory variation of the ballistocardiogram may result from altered cardiovascular dynamics. However, there are a number of factors which tend to reduce the significance of any index of respiratory variation in the evaluation of cardiac function. The pattern of respiration (rate, depth, and character of breathing), which may vary considerably from person to person, influences respiratory variation since the latter appears to be closely related to changes in intrathoracic pressure. The degree of respiratory variation may be easily altered by simply changing the rate and depth of breathing. Other factors which are believed to influence respiratory variation are changes in the pulmonary circulation, in the elasticity of the lungs, and in the amount of peripheral and splanchnic blood pooling.[18] The quantitative effects of these variables are difficult to assess in the individual patient.

The results of this study indicate that respiratory variation increases with age but they supply no explanation for this observation. Whether the increase in respiratory variation is due to myocardial "weakness" (produced by subclinical coronary artery disease or myocardial aging) or to other factors remains to be determined.

E. *Abdominal Compression.*—The effect of abdominal compression (30 mm. Hg) on the normal ballistocardiogram of the average subject can be briefly summarized as follows: The amplitude of the I wave is slightly decreased, while that of the J and K waves increased, the K more than the J; therefore, the ratio JK/IJ is considerably increased. IJ amplitude is increased by 17 per cent in the whole series. Respiratory variation in amplitude is reduced as indicated by an increase in "Ra" of 16 per cent.

There appears to be a "critical level" of pressure below which ballistic amplitude and form are improved and respiratory variation decreased but beyond which form deteriorates and amplitude decreases. In most of the normal subjects with normal records this "critical level" is above 30 mm. Hg, but in a few this degree of compression produces some form deterioration, usually of the I wave alone. Fig. 4 shows examples of the effect of abdominal compression on normal records.

Comment: Our interest in the effect of abdominal compression on the ballistocardiogram stemmed from Kerr and associates'[19] original finding that patients with angina pectoris are frequently improved symptomatically when they wear abdominal binders. Recently, Brown and associates[20] made similar observations on forty patients with angina pectoris whose ballistocardiograms

were improved by abdominal compression. deLalla and Brown[18] suggest that in certain cases coronary insufficiency may be secondary to a critically low left ventricular output caused by increased peripheral blood pooling and a consequent decreased "pulmonary pool." They reasoned that abdominal compression decreases respiratory variation and improves the symptoms of patients with angina pectoris by evacuating the splanchnic pool thereby, presumably, increasing the pulmonary pool and left ventricular output. In support of this concept they reported that following sympathectomy patients frequently show increased respiratory variation and form deterioration. These changes may be

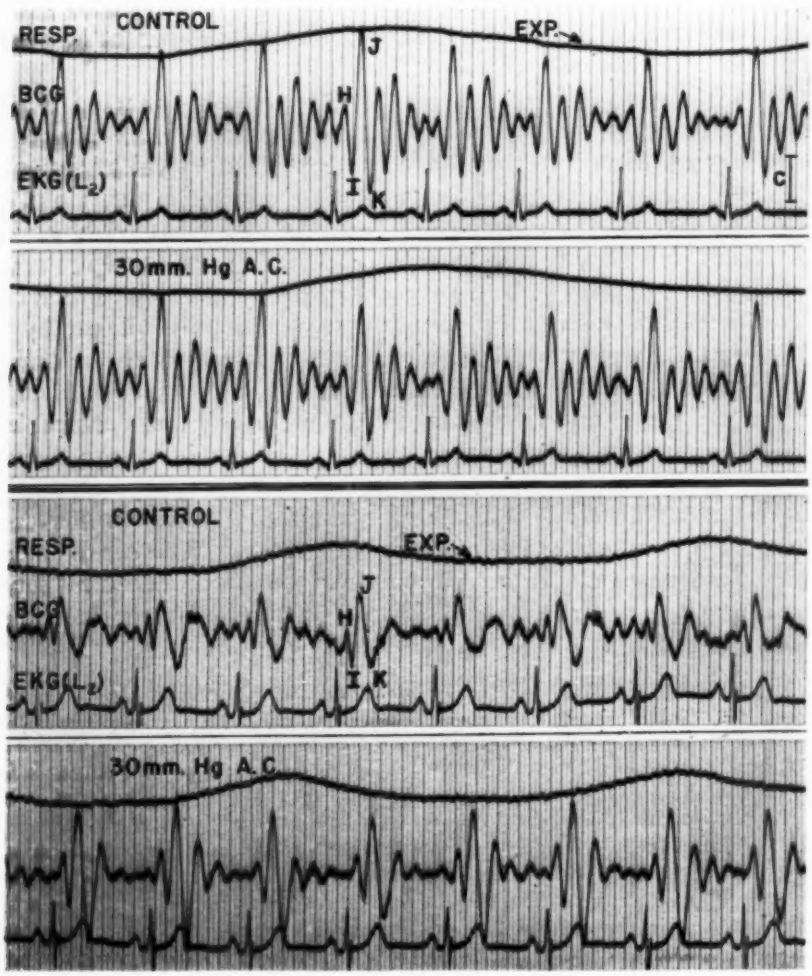
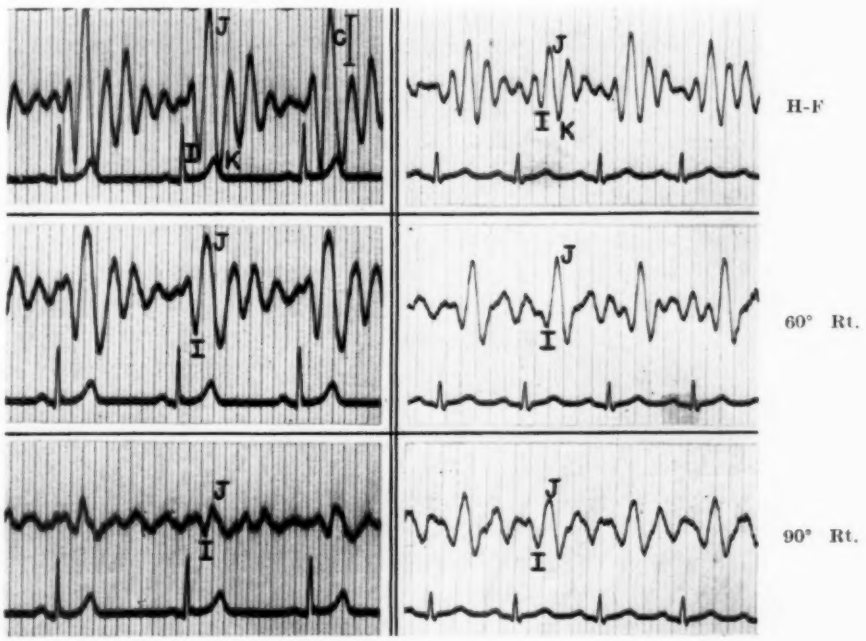


Fig. 4.—The effect of abdominal compression on normal ballistocardiograms. *A*, The control and abdominal compression (*A.C.*) records from a healthy 28-year-old man. The change in phase of respiration and ballistic amplitude, as shown here, occurs frequently. *B*, The records from a normal 58-year-old physician. Control record is normal but shows rather short I waves and slurred JK segments. Abdominal compression increases amplitude, improves form and greatly deepens the K waves.

In this and all subsequent Figs. the upper tracing is the pneumograph (*RESP.*). The middle tracing is the ballistocardiogram (*BCG.*), and the lower tracing is the electrocardiogram (*EKG.*). The bracketed vertical line marked *C* represents the 1 cm. deflection produced by the 280 Gm. calibrating weight and applies to all of the ballistocardiograms shown.

reversed when the peripheral pool is reduced by means of abdominal binders and elastic stockings.

The improvement in the ballistocardiogram produced by abdominal compression may, in fact, represent improvement in cardiovascular function but we have no objective evidence to prove it. The type of compression used in our study regularly produced changes in normal ballistocardiograms and frequently improved borderline and abnormal records. The procedure undoubtedly causes some compression of the abdominal aorta but the other physiologic mechanisms responsible for the changes are not yet known.



A. *B.*

Fig. 5.—The effect of age on ballistocardiographic vector records. *A*, Vector records from a normal 33-year-old man. Respiration suspended. IJ amplitude is great in the head-foot (*H-F*) record but small in the 90° rt. (lateral) record. *B*, Vector records from a normal 64-year-old man. Respiration suspended. The head-foot record is normal in form but IJ amplitude is somewhat less than in the 60° rt. record; at 90° rt. the complexes are tall and "normal" in form.

F. "*Vector*" *Records.*—The ratio IJ (lateral)/IJ (head-foot), which represents the ballistic frontal IJ axis, increases progressively with age; this is due less to an increase in IJ amplitude in the lateral record than to a decrease in IJ amplitude in the head-foot record. In some of the older normal subjects the IJ amplitude in the 60° rt. record is as great as, or greater than, that in the head-foot record but the lateral record is never as large as the head-foot. Fig. 5 shows the differing vector records in a young and in an old man.

An attempt was made to assess the effect of cardiac position on the frontal IJ axis, represented by the ratio IJ(lateral)/IJ(head-foot). Cardiac position was crudely defined by using both the electrocardiographic QRS axis and the anatomic long axis of the heart (from chest roentgenograms). The ratio IJ(lateral)/IJ(head-foot) increases progressively with age, indicating a clockwise rotation of the IJ axis in older subjects. Similarly, both the QRS and anatomic axes show progressive shifts with age, indicating more horizontal hearts in the older subjects. Since age

TABLE V. MEAN VALUES AND LIMITS (± 2 STANDARD DEVIATION) FOR CERTAIN BALLISTOCARDIOGRAPHIC MEASUREMENTS

A. TIME INTERVALS AND WAVE DURATIONS: 20 TO 69-YEAR-OLD MEN AND WOMEN

1. P-H Interval: 0.27 sec. (0.23–0.31)
2. Q-H Interval: 0.11 sec. (0.07–0.14)
3. Q-I Interval: 0.17 sec. (0.15–0.20)
4. Q-J Interval: 0.25 sec. (0.21–0.28)
5. Q-K Interval: 0.34 sec. (0.29–0.38)
6. Duration I Wave (I_t): 0.06 sec. (0.04–0.08)
7. Duration J Wave (J_t): 0.10 sec. (0.07–0.13)
8. Duration I & J Waves (IJ_t): 0.16 sec. (0.13–0.19)

B. AMPLITUDE MEASUREMENTS AND RATIOS: 20 to 69-YEAR-OLD SUBJECTS

1. Inspiratory IJ Amplitude (IJ_I):
   Men: 22.3 mm. (10.3–34.3)
   Women: 14.7 mm. (8.5–20.9)
2. Expiratory IJ Amplitude (IJ_E):
   Men: 14.9 mm. (5.3–20.2)
   Women: 10.3 mm. (4.9–15.7)
3. Mean IJ Amplitude (IJ_M):
   Men: 18.8 mm. (8.4–29.2)
   Women: 12.6 mm. (7.2–18.0)

or for a given age and sex, predicted value ± 2 S.D.

4. Ratio JK/IJ:
   Men: 1.07 (0.87–1.27)
   Women: 1.03 (0.93–1.13)
5. Ratio H_E/J_E:
   Men: 32% (0–64)
   Women: 25% (0–56)
6. IJ_E/IJ_I("Ra"):
   Men and Women: 68% (46–90)

or for a given age and sex, predicted value ± 2 S.D.

appeared to be related to all three variables, it was necessary to carry out partial correlations to eliminate the influence of age. The results indicate that there is no relation between the ballistic frontal IJ axis and the position of the heart within the chest (as defined by roentgenogram and electrocardiographic measurements).

Comment: Analysis of the ballistocardiographic vector records revealed that there is a progressive relative increase in the IJ amplitude of complexes in the 60° rt. and 90° rt. (lateral) records with aging. The significance of this observation is not clear. If aging produces a change in the spatial orientation of the vector loop, then records taken along the head-foot axis will obviously not be the same in older persons as in young ones. In some older subjects the 60° rt. records may more closely resemble the normal head-foot waveform than do the head-foot records, a finding which is even more striking in subjects with borderline or abnormal head-foot records (see below). This suggests that there has been a clockwise rotation (viewed from above the supine subject) of the whole vector loop. The finding of a clockwise rotation of the mean frontal IJ axis as age increases (in the subjects with normal records) supports this view. The change in the orientation of the vector loop with age cannot be accounted for by a change in the position of the heart with age. While it is true that there appears to be progressive shifts in both the anatomic cardiac axis and the frontal IJ axis with age they bear no relationship to each other when age is held constant. This supports conclusions drawn by Starr and Rawson[21] from their analysis of the contributions made by various parts of the cardiovascular system to the ballistocardiogram. They found that the movement of blood within the heart during systole played a minor role in the production of the ballistic complex. If this is true then the position of the heart within the chest, unless it is very abnormally placed, should have little influence on the orientation of the ballistic vector loop. Starr's studies indicated that the major contribution to the ballistic complex comes from the flow of blood within the aorta. Inasmuch as changes in the size and disposition of the aorta, for example, dilatation, uncoiling, and tortuosity, are known to occur with aging, the proposition that aortic factors are responsible for the orientation of the vector loop is a tempting one. Studies of the physical and physiologic aspects of this problem are currently under investigation.

G. *Summary of Analytic Results.*—In Table V are summarized the mean values and limits (±2 S.D.) for some of the measurements which may be useful in evaluating ballistocardiograms. On the basis of the results of this study, a set of preliminary, empirical criteria of normality for the ballistocardiogram may be set up. Subject to the qualifications which will be discussed below, a ballistocardiogram will not be considered normal if one or more of the following features are present:

1. Time Intervals and Wave Duration:
   Duration of I and J waves (IJ_t): Less than 0.11 or greater than 0.19 second.
   Others: Outside normal limits as defined in Table V.
2. Mean IJ Amplitude (IJ_M): More than 2 standard deviations below predicted value for age and sex (Fig. 2).
3. Ratio JK/IJ: Less than 0.85 or greater than 1.40 in men; less than 0.80 or greater than 1.30 in women, at any age.
4. Ratio H_E/J_E: Greater than 80 per cent in men and 70 per cent in women.
5. Ratio of Expiratory and Inspiratory IJ Amplitudes ("Ra"): More than 2 standard deviations below predicted value for age and sex (Fig. 3); or less than 40 per cent for any age or sex.

6. Ballistic Form:

a. Complete absence of the I, J or K waves in one or more complexes in each respiratory cycle.

b. Low amplitude of I or J wave with rounding, flattening or marked slurring in one or more complexes in each respiratory cycle.

c. Marked slurring of IJ or JK segments.

d. H wave taller than J wave in one or more complexes in each respiratory cycle.

There are a number of reservations regarding the use of these criteria. The series is not normally distributed with respect to age, being weighted with young subjects. Therefore, older subjects are not properly represented by the all-inclusive means and limits for those variables which are related to age. This is corrected in most cases by age regressions and these should be used when available. No regressions are given for Ratio JK/IJ or Ratio H_E/J_E, both of which are related to age, but the limits in the criteria above have been extended to include the older subjects. None of the quantitative criteria should be applied to records from individuals above the age of 60, nor should they be applied to individual ballistic complexes. The absolute amplitude values can be used for other high-frequency ballistocardiograph beds only when mean amplitude values from the other beds are comparable to our values for similar age and sex groups.

In the interpretation of the ballistocardiogram attention should be given to the recurrent abnormality, not the occasional one. Artifacts are more frequent and less easy to identify in the ballistocardiogram than in the electrocardiogram. Interpretation should be based on the complexes inscribed during ordinary quiet breathing; if an abnormality is significant it usually recurs in each respiratory cycle. A method for simultaneously recording the phase of respiration is highly desirable and a timing device (electrocardiogram or carotid pulse) is imperative for ballistocardiographic interpretation.

III. *Results of Analysis of Borderline Ballistocardiograms.*

There were thirty-three ballistocardiograms classified as borderline among the total of 369 records (9.0 per cent). Two of these were in persons in the fourth decade and the remaining thirty-one were in subjects over 40. The average age of the group was 53 years. The electrocardiogram was not abnormal in any of these cases and was borderline in only two.

A. *Qualitative Evaluation of Wave Form.*—Considerable importance is attached to the analysis of borderline ballistocardiograms because these form a transition between normal and abnormal records and should show early changes which in more exaggerated form characterize abnormal records.

Certain generalizations may be made from inspection of the borderline records. These records usually show complexes which are normal during inspiration but altered in form and amplitude during expiration. One of the most striking features of the borderline group was the increased variation in ballistic amplitude during respiration. Sixty per cent of these records showed moderate form changes in some of the expiratory complexes, while 20 per cent showed rather marked form changes. The most frequent alteration was one in which the expiratory H wave was relatively prominent and the J relatively short. This varied from a minor trend to the classical "early M" form (prominent H, short I, and low J waves). Many of the borderline records showed normal I, J, and K waves but relatively prominent H waves during expiration.

The "late downstroke" pattern (small or absent I, very low J, and deep K waves) was uncommon and, in its "classical" form, occurred in only one record. However, the trend toward

small I waves and deep K waves in some complexes was noted in almost one-half of the cases. Variants of the "late downstroke" and "early M" forms were sometimes present in different complexes in the same record and were also seen to coexist in the same complex (prominent H, small I and J, and deep K waves). There were small, "doubled" or otherwise deformed J waves in about one-third of the records. The K wave was wide, slurred, or otherwise deformed in about the same number. Taking all types together an average of about one out of every five complexes was considered to be "abnormal" on an empirical, qualitative basis.

An analysis of the ballistic complexes inscribed with respiration suspended in the midposition revealed that in three-fourths of the cases there was distinct general improvement in form and in over one-half it became entirely normal. Abdominal compression produced even more remarkable improvement. Ninety per cent were greatly improved, 50 per cent were rendered entirely normal while only 7 per cent were made worse by this procedure.

In the ballistocardiographic vector records normal or near normal records in the 60° rt. position were not uncommon. The presence of abnormal expiratory complexes in the head-foot records but normal expiratory complexes in the 60° rt. record was sometimes striking; the amplitude of the complexes in these vector records was comparable to that in the head-foot records. Fig. 6 shows two borderline head-foot records with the corresponding vector and abdominal compression records.

B. *Statistical Differences Between Normal and Borderline Ballistocardiograms.*—The borderline records were subjected to the same detailed analysis as were the normal ones. In order to achieve comparability and statistical validity only the twenty-two men in the fifth and sixth decades with borderline records were grouped together for the calculation of mean values. These were compared with the fifty-nine men in the same decades with normal records. The two groups were comparable in all respects except pulse rate and this difference, though significant, was small.

In general the results of this study served to verify the qualitative generalizations previously made. The major differences between these two groups were the greater respiratory variation in amplitude and the partial deterioration of the expiratory complexes in the borderline records. Absolute inspiratory I and J wave amplitudes were similar in both groups but the amplitudes of the expiratory I, J, and K waves were all significantly smaller in the borderline group. There was much greater respiratory variation in the borderline records than in the normal ones; for each of the three respiratory variation indexes there were significant differences between the two groups. The difference was most significant for "Ra" (d/S.E. = 5.0) and least significant for R.V.I. (d/S. E. = 3.8). In the borderline records the average expiratory IJ amplitude was less than one-half that of the inspiratory, that is, "Ra" less than 50 per cent. There was no significant difference in the absolute amplitude of the H wave but there was for the ratio H_E/J_E; this resulted from a reduction in the J wave in the borderline group and is a manifestation of the tendency toward the "early M" pattern.

Abdominal compression produced an increase in IJ amplitude in the borderline records comparable to that noted in the normals. A marked decrease in respiratory variation was produced by this procedure. The ratio of IJ amplitudes ("Ra") increased 50 per cent in the borderline group as opposed to an increase of 22 per cent in the normal group.

IV. *Abnormal Ballistocardiograms.*

Of the 369 normal subjects, ninety-three (25.2 per cent) had abnormal ballistocardiograms. The increasing frequency of abnormal ballistocardiograms with age is evident from the data presented in Fig. 1 and in Table I. Among the

214 subjects below the age of 50 there were abnormal records in only eight (3.7 per cent) whereas among the 155 subjects above the age of 50 there were abnormal records in eighty-five (54.8 per cent). Among the ninety-three individuals with an abnormal ballistocardiogram, the electrocardiogram was abnormal in 9.7 per cent, borderline in 20.3 per cent and normal in 70 per cent.

The abnormal ballistocardiograms, which did not lend themselves to quantitation, were not subjected to detailed analysis. However, certain generalizations about form abnormality may be made from them.

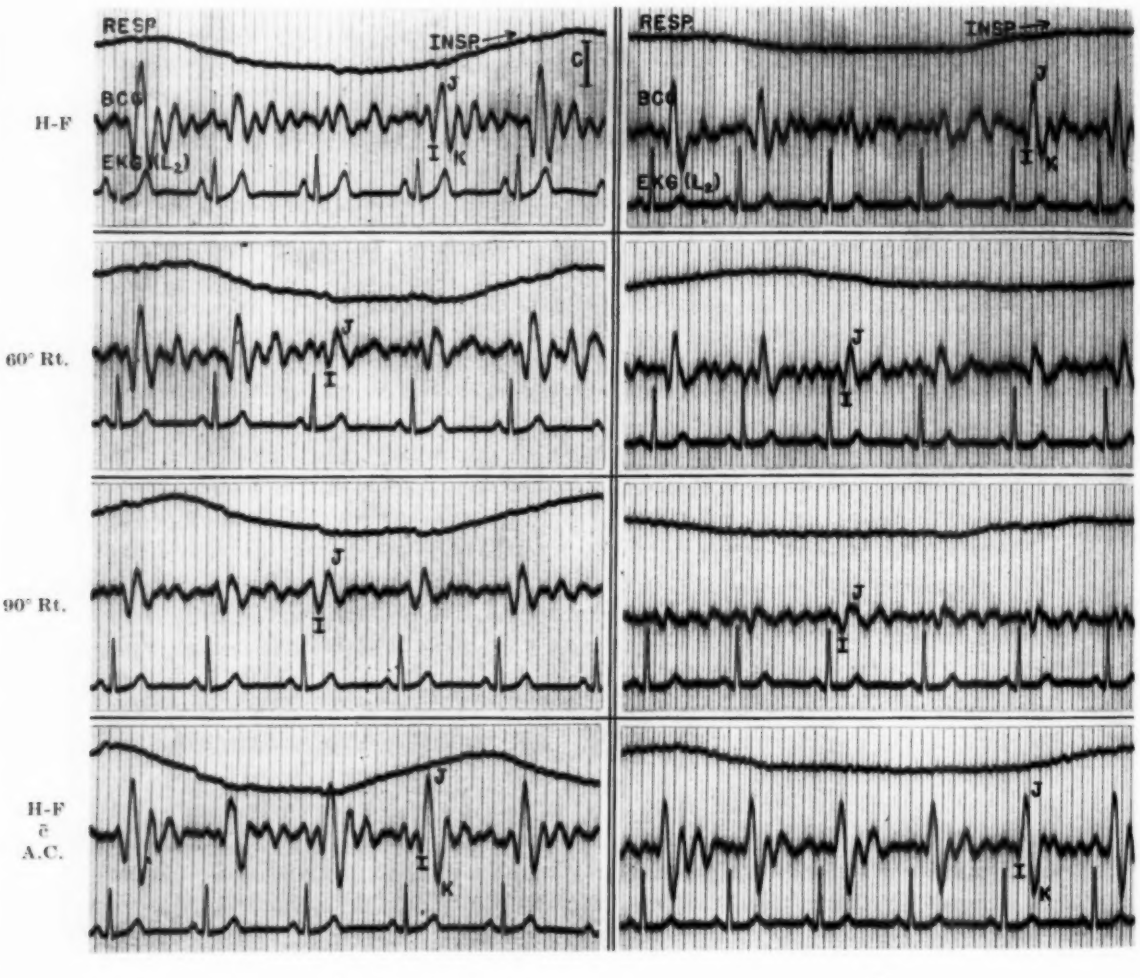


Fig. 6.—Borderline ballistocardiograms. In *A* and *B* are shown the vector ballistocardiograms and the abdominal compression records from two clinically normal subjects. Both head-foot (*H-F*) records show marked respiratory variation and small expiratory complexes with I waves which scarcely descend below the baseline. The 60° rt. vector records in both are more "normal" than the head-foot record and show less respiratory variation. Abdominal compression (*A.C.*) increases ballistic amplitude, reduces respiratory variation, and deepens the K waves; however, in *B*, the I waves are practically obliterated by compression (60 mm. Hg in this case).

Qualitative Evaluation of Wave Form.—It should be recognized that there is no single common pattern in the abnormal ballistocardiograms from older normal persons. Some records show abnormal complexes of a single specific type, some show mixtures of several types and others show no recognizable, repetitive type. A single complex may demonstrate characteristics of two types, for example, a combination of the early M and late downstroke tendencies. The most common single type of abnormality encountered in this group was the early M form and its variants.

Ballistocardiographic form may be abnormal in many different respects. Considering the systolic waves (H, I, J, K) alone, the I and/or J waves may be very small, leaving the H and/or K waves relatively prominent; or there may be an absolute increase in the amplitudes of the H and/or K waves. Aside from amplitude changes the systolic waves may show notching, slurring, rounding, or doubling; in some cases no systolic waves can be identified. The systolic complex, particularly its earlier part, may be distorted by ride-in from deflections arising in presystole. There may be large diastolic waves which exceed those in systole and dominate the record.

Although a few records are bizarre and show no consistently recurring pattern, the majority of abnormal records do show some degree of consistency in wave form. Complexes occupying the same temporal position in different respiratory cycles are usually closely similar in form. In follow-up studies it was found that the earliest trend toward abnormality in a previously normal record is usually an alteration of a single expiratory complex. As the abnormality progresses, more and more expiratory complexes become affected and finally the inspiratory complexes, one after another, become abnormal, leaving no normal complexes during any phase of respiration. The importance of respiration on ballistic form is clearly demonstrated by the finding that records which are distinctly abnormal during ordinary breathing may become surprisingly normal when respiration is suspended. However, this usually is found in those records with lesser degrees of abnormality and is uncommon in the ones with marked abnormality.

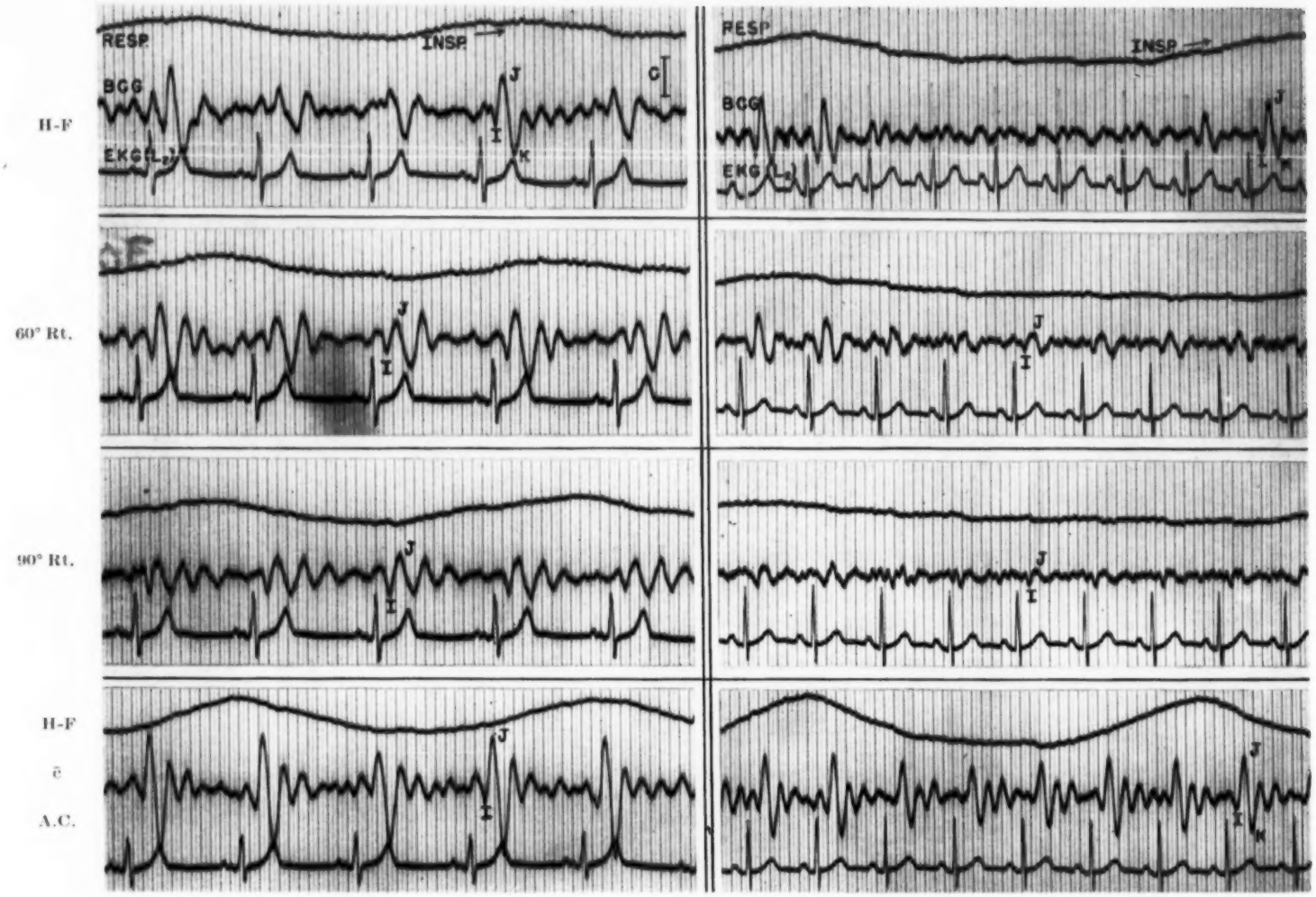
Abdominal compression often greatly improves ballistic form, decreases respiratory variation, and increases amplitude in abnormal records, sometimes rendering them normal. However, in some cases this procedure has no particular effect and in others it renders form even more abnormal.

The vector records in these subjects with abnormal head-foot ballistocardiograms were of interest. Earlier it was indicated that normal and borderline records from older individuals showed a tendency toward increase in the IJ amplitude in the 60° rt. and 90° rt. (lateral) vector records relative to the IJ amplitude in the head-foot record, that is, a clockwise rotation of the frontal IJ axis. The same tendency is manifest in the abnormal records. While no attempt will be made here to describe the various vector patterns encountered, one finding is worthy of comment. In the presence of an abnormal head-foot record the 60° rt. or lateral records may be normal in form, and the amplitude of the expiratory complexes in these records may be several times as great as that in the head-foot record. Fig. 7, A illustrates this point. On the other hand, many cases, such as that of Fig. 7, B, have vector records which do not show normal complexes.

DISCUSSION

The most striking finding in this study was the surprisingly high incidence of abnormal ballistocardiograms in apparently normal persons above the age of 50. Abnormal records were present in only 4 per cent of the subjects below 50 but in 55 per cent of those above this age. Direct comparison of our results with those of Dock and associates[9] and of Taymor and associates[12] is not possible because these investigators used different methods of form classification and/or included postexercise records in their evaluation of ballistocardiographic form. However, all three studies are in good general agreement on the increasing incidence of abnormal ballistocardiograms in aging normal persons.

We have termed the individuals in our control group "apparently normal" because they satisfied the criteria we set up for normality, criteria which are generally accepted in the clinical evaluation of cardiovascular function. Yet it is likely that these criteria are not stringent enough because there are a number of



A. *B.*

Fig. 7.—Abnormal ballistocardiograms. *A*, 73-year-old clinically normal physician. Head-foot (*H-F*) record shows one normal complex in inspiration; remaining complexes are abnormal and show absent I waves, low J waves and deep K waves. 60° rt. and 90° rt. vector records show relatively large, well-formed IJK complexes. 30 mm. Hg abdominal compression (*A.C.*) increases amplitude, reduces respiratory variation and improves form (although K waves become quite deep). *B*, 56-year-old healthy nurse. In the head-foot record during expiration ballistic complexes practically disappear and waves are not identifiable. Amplitude of complexes in vector records is also small. Abdominal compression increases amplitude, reduces respiratory variation and improves the form of the expiratory complexes.

abnormalities of the heart and circulation which may not be detectable by the usual methods of clinical examination. One of the most important of these is coronary artery disease, a condition which usually does not reveal itself by symptoms and signs until it has become far advanced pathologically. The frequency with which coronary sclerosis is found at autopsy in individuals who have died of noncardiac causes makes it apparent that this condition is an almost universal one in persons above the age of 40 years. White, Edwards, and Dry[22] have shown that a severe degree of coronary atherosclerosis is present in the majority of individuals above the age of 50; even in their 30 to 39-year age group, 18 per cent of the individuals demonstrated severe coronary sclerosis. It is evident then that coronary artery disease occurs quite frequently in the so-called normal adult population and is difficult or impossible to detect with the usual clinical diagnostic methods.

The proposition that the abnormal ballistocardiograms from normal individuals result from subclinical coronary atherosclerosis is a compelling one. Three of Starr's four apparently normal subjects with abnormal ballistocardiograms subsequently developed angina pectoris or myocardial infarction.[13] The curve representing the increasing incidence of ballistocardiographic abnormality with age roughly parallels that of White, Edwards, and Dry[22] for the increasing incidence of severe coronary atherosclerosis with age* and is similar to other age incidence curves for clinical coronary artery disease and for deaths due to coronary atherosclerosis.[23] Furthermore the great majority of patients with clinical coronary artery disease have abnormal ballistocardiograms and these records do not appear to be qualitatively different from the abnormal records of our older normal persons. While these facts are suggestive they do not provide conclusive proof for a causal relationship between ballistocardiographic form abnormality and coronary artery disease in clinically normal persons. One cannot exclude the possibility that the heart muscle shares in the same degenerative changes, independent of atherosclerosis, that take place in other organ-systems as the human body grows older. Indeed, Dock[24] has pointed to myocardial aging as a specific clinical entity on which he conferred the name "presbycardia."

Aside from purely cardiac causes, a number of extracardiac factors are believed to play a role in producing the ballistocardiographic abnormality observed in aging normal persons. Among these may be mentioned changes in the size and elasticity of the aorta and the larger arterial branches, changes in the lungs and pulmonary circulation, and peripheral and splanchnic blood pooling. If the effects of these extracardiac factors on ballistic form could be identified and separated, a sounder evaluation of cardiac function would be possible; until these factors can be separated it should not be assumed that the ballistocardiographic abnormality in clinically normal persons indicates coronary artery disease.

Starr has contributed much along the two lines of approach which seem the most promising, namely, clinical follow-up and physiologic research. Much remains to be done before the ballistocardiograph can be offered with assurance as a routine tool for the evaluation of clinical cardiovascular problems. For the

*One point of difference between the two curves is that White's reaches a peak in the sixth decade and levels off whereas our curve continues to rise in the older groups.

present, the ballistocardiograph should be treated with the same clinical caution accorded other new diagnostic methods. If the ballistocardiographic interpretation coincides with the other clinical and laboratory data, then it may be given weight. On the other hand, if the ballistocardiogram is abnormal in the absence of any other confirmatory findings one should reserve opinion on its clinical significance. Until some of the more basic problems are solved the ballistocardiograph should be considered primarily an investigative tool, one which will undoubtedly be of great importance in the future.

SUMMARY

1. Ballistocardiographic and electrocardiographic studies were made on 369 clinically normal persons from 20 to 84 years of age. The frequency of abnormal, borderline, and normal records was determined for each age-decade group.

2. A detailed quantitative analysis was made of approximately sixty variables from 275 normal and borderline ballistocardiograms.

a. A study was made of some of the factors influencing the amplitude and duration of the ballistic complex, respiratory variation, cardiac output, ballistic "vector" distribution, and other ballistocardiographic variables.

b. Regression equations were set up for some of the measurements which were significantly correlated with age, pulse rate, body size, or other factors.

c. Mean values and limits were defined for some of the measurements used in evaluating the ballistocardiogram.

d. Preliminary, empirical criteria of normality for the ballistocardiogram were submitted.

3. The borderline and abnormal ballistocardiograms were analyzed qualitatively.

4. The high incidence of abnormal ballistocardiograms from clinically normal persons in the older age groups was pointed out. The need for caution in attributing clinical significance to these records was stressed.

The authors wish to thank Dr. Edward Wiss, who rendered assistance in early phases of this work and to Dr. Margaret Merrill, of the Department of Biostatistics, for reviewing the statistical handling of the data. Gratitude is also expressed to the many members of the professional and nursing staffs who kindly volunteered to serve as normal subjects for this study.

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BILHARZIAL COR PULMONALE

A Clinicopathologic Report of Two Cases

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EVER since Sorour,[1] Azmy and Effat,[2] and later on Shaw and Ghareeb[3] reported their studies on pulmonary schistosomiasis, this subject has received a good deal of interest in Egypt because of the frequency with which pulmonary heart disease due to Bilharzia is met with in hospital practice. But, while so many clinical and radiologic accounts of the condition have been reported, only relatively few necropsy studies have been recorded. This is mainly due to the fact that the patients come from the country to the main hospitals for medical help and usually insist on going to their homes if their condition deteriorates. So far, only twelve autopsies have been reported in the English literature. It is felt that recording these two cases helps to throw more light on the subject.

Case 1. (M.M.K.).—A 29-year-old man whose occupation was farming came to the hospital complaining that he felt pain in the sternal region both on effort and at rest; he also complained of dyspnea on exertion. The patient had been subject to this pain for the previous five years, but the condition had become much worse during the latter ten months. There was no history of rheumatism or syphilis but the patient stated that he had bilharziasis of the urinary and intestinal tracts.

On examination a mild degree of cyanosis and shortness of breath, on lying down flat, was noticed. When propped up to an angle of 45 degrees, the neck veins filled to a level of 7 cm. above the sternal angle and showed distinct aV pulsations. The pulse was normal, the blood pressure 120/80 mm. Hg and the chest was emphysematous. The apex beat was felt in the fifth intercostal space 5 inches from the midsternal line and was of a tapping character; distinct right ventricular pulsations were felt in the third and fourth left intercostal spaces. The closure of the pulmonary cusps was not felt, but the second left intercostal space was dull to percussion. The cardiac sounds were distant at the apex, and a wide splitting of the second heart sound with accentuation of its second component was heard over the base. A harsh systolic murmur was heard over the apex and at the second left intercostal space; a short mitral diastolic murmur was also heard over the apex. There was no pulmonary incompetence. The liver was enlarged four fingerbreadths below the costal margin; it was firm, slightly tender, and showed marked systolic pulsations; the spleen was felt four fingerbreadths down and was firm but not tender. Fluoroscopy showed a heart that was markedly enlarged, the right ventricle being the chamber mainly involved. The left ventricle was of normal size. The pulmonary artery and its two main branches were moderately dilated but showed no abnormal degree of pulsation. Radiography confirmed these findings.

The electrocardiogram showed a partial right bundle branch block with an inverted T wave in Lead III and in the right ventricular surface leads.

The patient died after a severe hematemesis.

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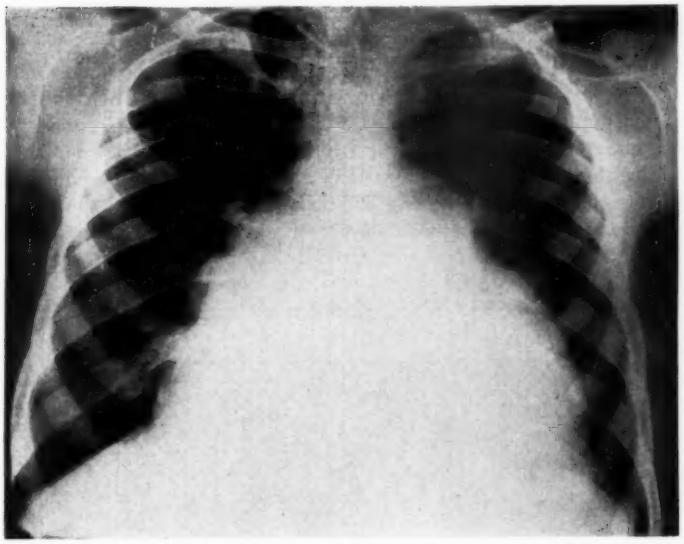

Fig. 1 (Case 1).—Posteroanterior view showing a marked degree of cardiac enlargement with a steep left border and a dilated pulmonary artery.

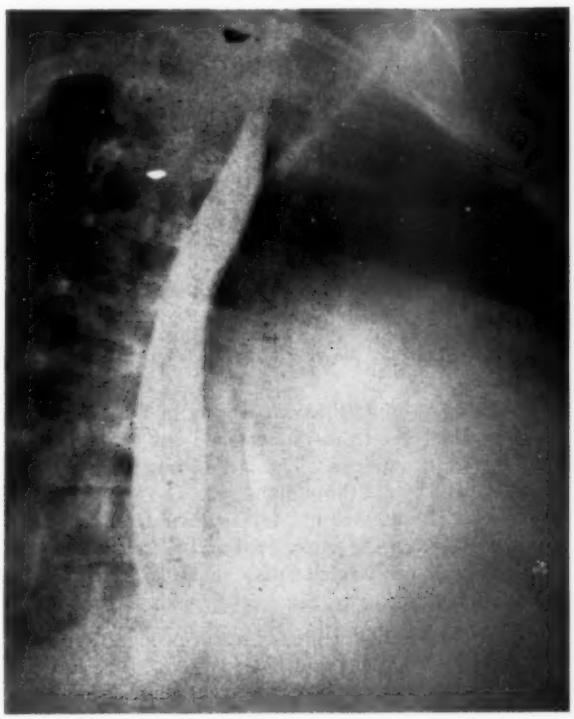

Fig. 2 (Case 1).—Right oblique view with a barium swallow showing the impression caused by the pulmonary artery. The left auricle is of normal size.

Autopsy.—The pericardial sac contained 100 c.c. of straw-colored effusion and there were no pericardial adhesions. The heart weighed 750 grams, the enlargement having especially involved the right side. The pulmonary artery was moderately dilated; its circumference above the valve measured 9 cm.; its cusps were healthy, and its intima was smooth. The right ventricle measured 0.9 cm. in thickness and its cavity was dilated. The right auricle was also moderately dilated and both interatrial and interventricular septa were intact. The circumference of the aorta was 6 cm. Its intima was healthy. Both the left ventricle and the left auricle were normal. The lungs showed a moderate degree of emphysema but no appreciable edema; the pulmonary branches showed no atheromatous changes, a moderate degree of thickening of their walls, and on section no miliary bilharzial tubercles could be seen around the small arterioles. There was no evidence of pulmonary embolism. Large esophageal varicose veins were present. The liver weighed 1,750 grams. Its outer surface was irregular; its cut surface was yellowish green, and its portal

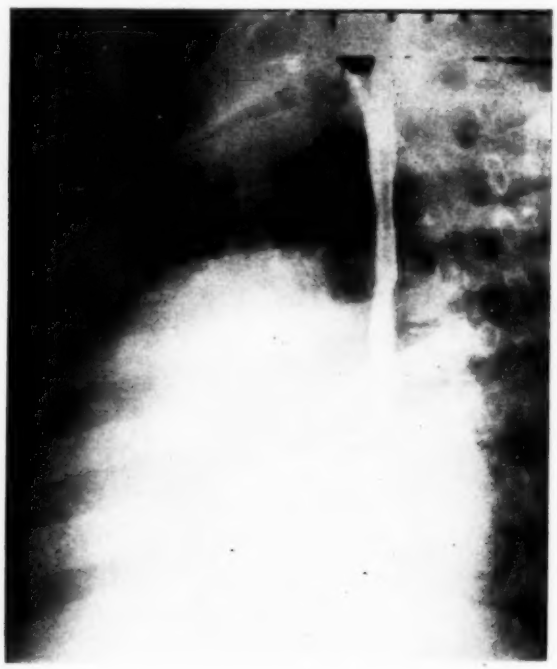

Fig. 3 (Case 1).—Left oblique view showing an enlarged right ventricle.

tracts were thickened. There were no Bilharzia worms in the portal blood. The spleen and splenulus present with it weighed 750 grams; its capsule was smooth; its cut surface congested, and its fibrous trabeculae were prominent. The large intestine, particularly the rectum, contained a heavy deposit of calcified ova in the submucosa. The appendix was heavily studded with Bilharzia ova in all its coats. The ureters and urinary bladder showed the characteristic sandy patches formed by deposits of ova in the submucosa and a scraping of these yielded ova of Bilharzia hematobium. The seminal vesicles felt gritty on cutting through them with the knife and contained a large number of the same ova.

Histology.—The lungs showed a mild degree of passive congestion and a moderate number of parenchymatous tubercles of fairly recent and healed types. The healed tubercles were extravascular areas of scar tissue, some with calcified ova in the center while the more recent ones were formed mainly of collections of lymphocytes around the ova. No ova with their embryo undergoing destruction by giant cells were seen, and no recent tubercles showing mobile histiocytes and eosinophilic leukocytes were present either. These findings are commonly seen in patients, with a

mild but long-standing bilharzial infestation either of the urinary or intestinal tracts, who have constant emboli to the pulmonary arterioles with Bilharzia ova. Angiomas were present in moderate number; they were mostly small and of the capillary type. Only a moderate degree of medial hypertrophy of the pulmonary arterioles was seen. The pulmonary artery had a healthy intima but its media was hypertrophied. The cardiac muscle showed cloudy swelling but no Bilharzia ova were seen in sections taken from both ventricles.

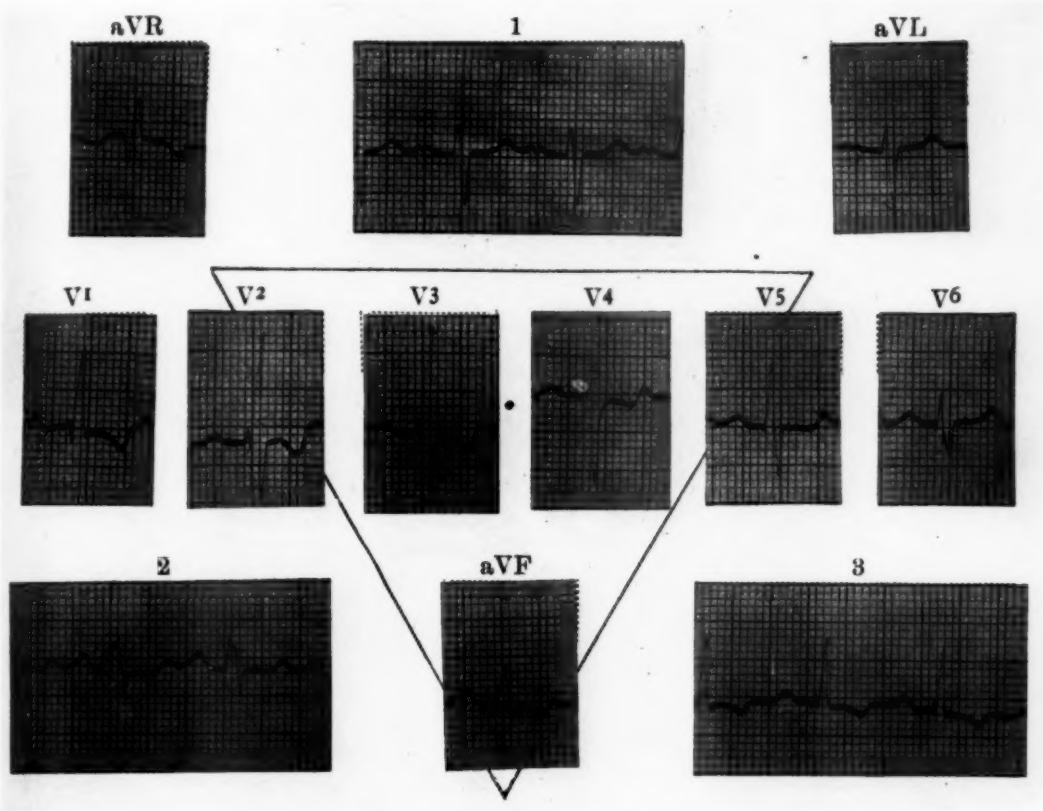

Fig. 4 (Case 1).—Electrocardiogram showing a partial right bundle branch block with an inverted T wave in the right ventricular surface leads.

CASE 2. (M.A.S.).—A man aged 32 (previously reported by Girgis[4]) was admitted to the hospital complaining of dyspnea on effort, dry cough, and edema of the legs. He had been short of breath for two years, but the edema had appeared only one month before he came to seek advice. He gave a history of having been treated three times for urinary and intestinal bilharziasis during the second decade of life.

Examination showed a moderately built man with a slight venous congestion in the neck and a little edema of the legs, but no cyanosis. The heart was moderately enlarged to the left, pulsations were seen and felt in the third, fourth, and fifth intercostal spaces, and a diastolic shock was felt in the second left intercostal space. The auricle was fibrillating and the second sound was markedly accentuated in the pulmonary area. A systolic murmur was heard at the apex, and in the pulmonary area a systolic murmur and an early diastolic murmur were heard. The liver was markedly enlarged and firm; it was slightly tender. The spleen was also markedly enlarged. The chest was emphysematous and râles could be heard over both bases.

Fig. 5.

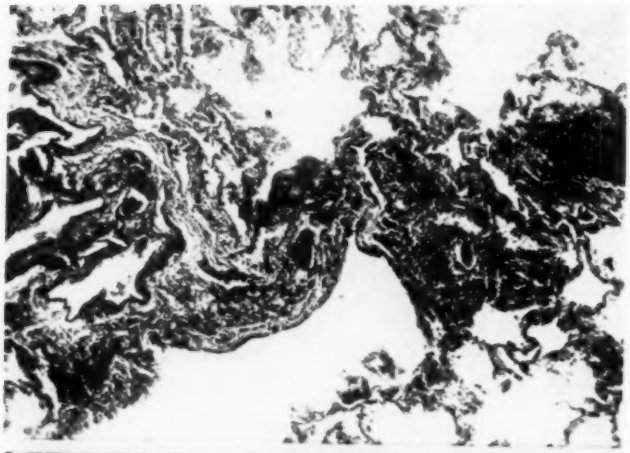

Fig. 6.

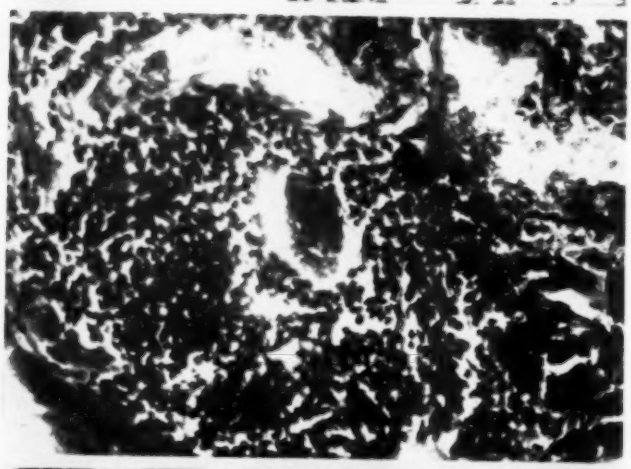

Fig. 7.

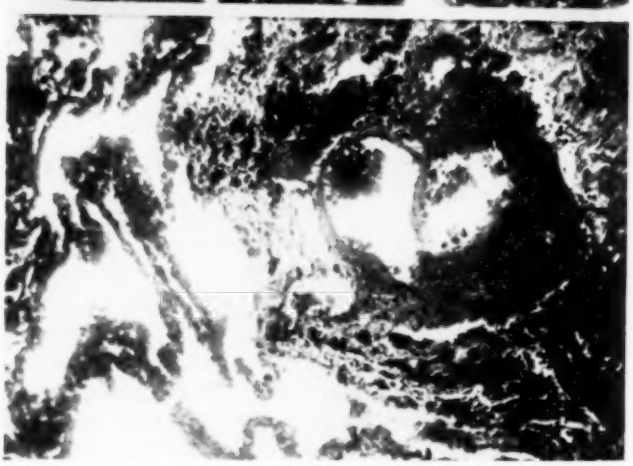

Fig. 5 (Case 1).—Section of lung showing a Bilharzia ovum surrounded by lymphocytes and lying outside a young angioma. The latter is composed of capillary and cavernous spaces. ×60.

Fig 6 (Case 1).—The ovum and surrounding lymphocytes in Fig. 5 seen with a higher magnification. ×210.

Fig. 7 (Case 1).—Recanalization of an obliterated arteriole. ×160.

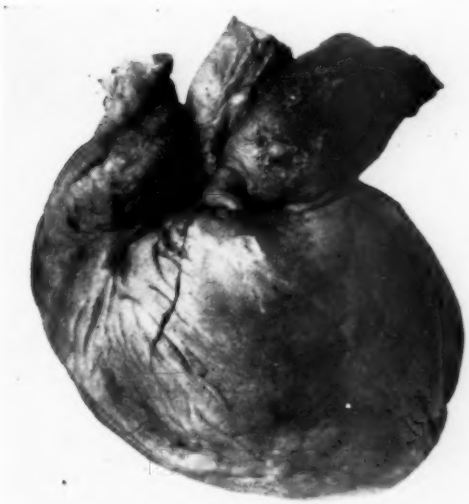

Fig. 8 (Case 2).—Anterior aspect of heart and big vessels. The right ventricle forms the whole anterior cardiac surface as well as left border and the pulmonary artery is about twice as big as the aorta.

Fig. 9.

Fig. 10.

Fig. 9 (Case 2).—Right ventricle and pulmonary artery and its right and left branches. Note the thickness of the wall of the ventricle and the atheromatous changes of the intima of the arteries.

Fig. 10 (Case 2).—The left ventricle and aorta for comparison with Fig. 9.

The roentgenogram showed right ventricular hypertrophy and dilatation of the pulmonary artery and its branches. (Hilar pulsations could hardly be detected on fluoroscopy.) The blood picture was normal. The Wassermann reaction was negative, and the blood pressure was 120/85 mm. Hg. The electrocardiogram showed right ventricular hypertrophy and auricular fibrillation.

Cardiac catheterization showed a pulmonary artery pressure of 60 mm. Hg and no evidence of arteriovenous shunt.

The patient died of congestive heart failure.

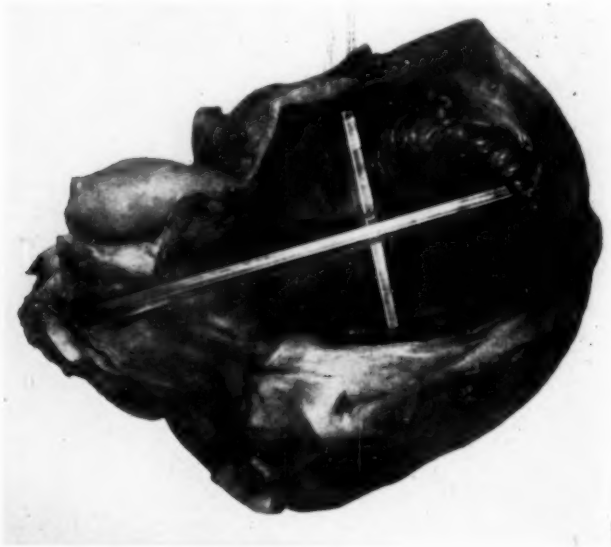

Fig. 11 (Case 2).—The right auricle seen from above to show the wide tricuspid valve to the right and the intact interatrial septum to the left.

Autopsy.—The heart weighed 500 grams and its whole anterior surface as well as the apex were formed by the right ventricle. The dilated pulmonary artery looked twice as big as the aorta, its circumference being 8 cm. above its cusps, 10.5 cm. at a distance of 5 cm. above the cusps, and 8.5 cm. at its point of bifurcation. The two main branches of the pulmonary artery were markedly dilated, the right having a circumference of 7 cm. at its origin and the left 6.5 cm. The walls of these three vessels were thickened, and their intima was covered by atheromatous plaques. The circumference of the aorta above its cusps was 5.5 cm., and its wall was normal and showed no atheromatous changes. The right ventricle had a thickness of 1.1 cm.; the tricuspid valve admitted three fingers freely; the right auricle was markedly dilated. Both interatrial and interventricular septa were intact. The left ventricle had a thickness of 1 cm., the mitral ring admitted two fingers; the left auricle was of normal size. The lungs were congested and the thick-walled branches of the pulmonary artery seen in section were sclerosed and presented the silver-wire appearance described by Shaw and Ghareeb.[3] The liver weighed 1,500 grams, was congested, and its surface showed flat-topped elevations separated by wide shallow depressions. On section its portal tracts were markedly thickened; its color was rusty brown, and it was firm in consistency. The spleen weighed 750 grams, was firm in consistency, and its capsule showed patchy thickening. On section its pulp was dark red in color, and the lymphoid follicles were atrophied and replaced by pin-point, greyish-white dots. The trabeculae were thin and protruded.

Histology.—Sections from both lungs were examined. The medium-sized pulmonary arterioles showed a marked degree of hypertrophy of their media while obliterative arteriolitis was seen in a good number of the smaller arterioles. A large number of cavernous angiomas were also seen. Calcified ova taking the hematoxylin stain were seen in close relation to the pulmonary

arterioles but there were no pulmonary changes suggestive of recent embolism. The trunk and two main branches of the pulmonary artery showed a marked degree of medial hypertrophy and their intima was the seat of extensive atheromatous changes with calcification in some areas. The aorta and sections from both ventricles were normal. The liver showed an advanced degree of periportal cirrhosis, but no Bilharzia ova were seen on section. The spleen presented the usual picture of bilharzial splenomegaly. The rectum showed calcified deposits of ova in the submucosa.

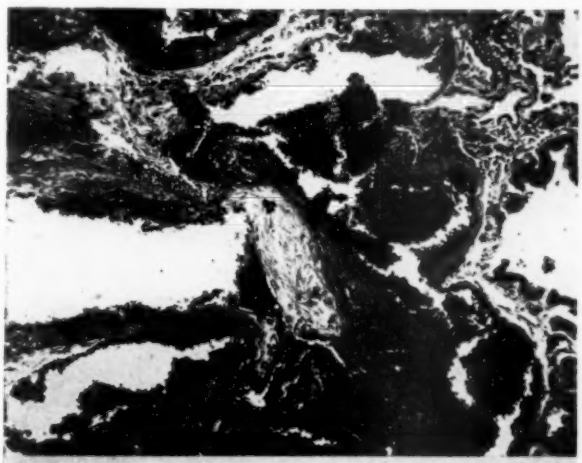

Fig. 12.

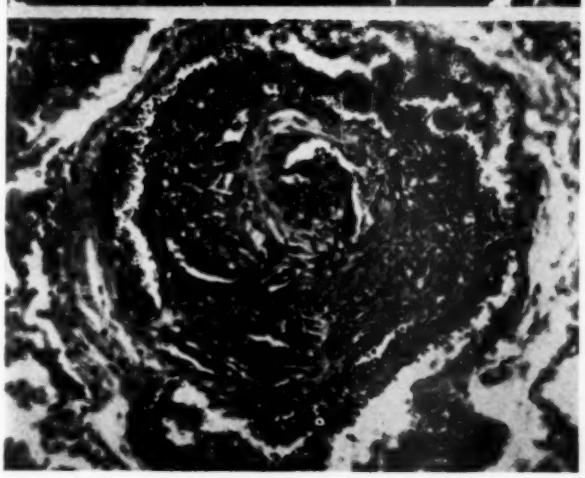

Fig. 13.

Fig. 12 (Case 2).—A mature cavernous angioma just outside a pulmonary arteriole. ×160.
Fig. 13 (Case 2).—An obliterated arteriole showing a marked degree of myohypertrophy. ×160.

DISCUSSION

Right-sided cardiac hypertrophy and strain following pulmonary endarteritis is now an established entity. It is felt among those familiar with the condition that the best name to give it is "Bilharzial cor pulmonale." This name helps to do away with inaccurate and redundant terms like "Bilharzial Ayerza's disease" or the "Syndrome of cardiopulmonary bilharziasis" that are still used sometimes to describe these cases, and which might impart the idea that its clinical picture is still blurred, or that it includes more than one defined entity.

Taking into consideration the fact that one-half the twenty million Egyptians are suffering from bilharziasis, and yet out of 1,000 cardiac patients seen by Girgis and Baragan[5] only twenty cases of bilharzial cor pulmonale were met with, it becomes evident that certain factors must be present that determine which of these bilharzial patients are destined to develop that cardiac state. One of us is familiar with the fact that patients with bilharzial cor pulmonale are usually either free from or only suffer a mild bilharzial infection of the urinary or intestinal tracts or both. This is to be expected, when it is realized that a patient with a heavy bilharzial infection seeks speedy medical help to relieve his urinary or intestinal symptoms, while the patient with a mild infection is likely to neglect it. Also judging from the rate of cure obtained by Girgis and Aziz[6] and by Girgis and Magid[7] in bilharzial patients and by the fact that one-third of their cases were found harboring living worms months after the end of antimony treatment, it seems likely that those patients who start with a heavy infection, receive treatment, and end with a mild chronic infection are those liable to develop the cardiac complication.

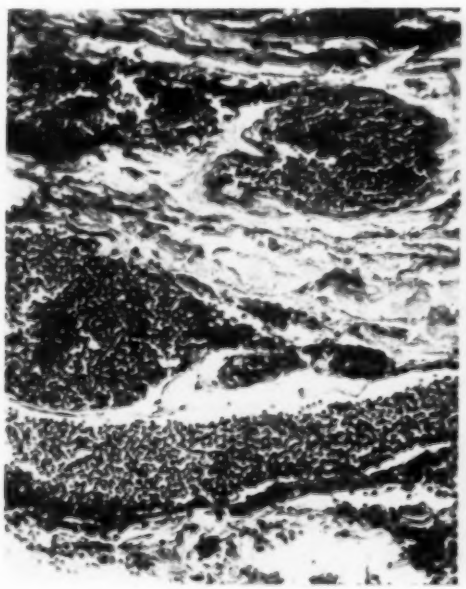

Fig. 14.

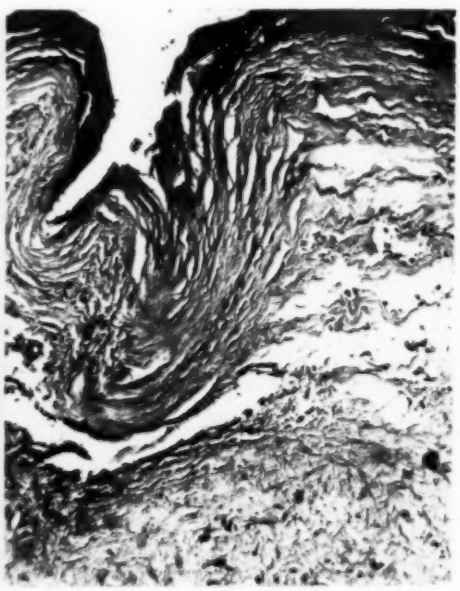

Fig. 15.

Fig. 14 (Case 2).—The intima and a part of the media of the pulmonary artery. Note the thickening of the intima with calcification in parts of the subintimal layer. ×210.

Fig. 15 (Case 2).—The adventitia of the pulmonary artery showing the large-sized vasa vasorum. ×210.

A point that has attracted attention is the angiomas that are seen in sections taken from the lungs of cases of bilharzial cor pulmonale. Clark and Graef[8] were the first to recognize the obliteration of the lumen of the pulmonary arterioles by a richly vascularized tissue resulting from canalization without previous thrombosis. The presence of angiomas was described by Shaw and Ghareeb[3]

who considered them as adaptations to overcome the obstruction to the pulmonary circulation. They thought that the growth in size of the blood spaces to cavernous dimensions beyond the confines of the original vessels was due to the loss of the controlling effect of the media of the arteries in which they develop. As fully developed angiomas identical with those seen in bilharzial cor pulmonale are also seen in cases of primary pulmonary hypertension, it seems more likely that the angiomas are only dilated anastomatic channels that develop between the pulmonary and bronchial vessels to relieve the raised pulmonary pressure and not the dilated capillaries of canalization. Another pathologic change in this condition is that of calcification of the pulmonary arteries. Evidently a marked degree of this process does not take place, and only slight calcification of the degenerated subintimal layer is met with in pathologic studies. This explains the fact why calcification of these vessels is not seen radiologically. It is also significant that while in syphilitic aortitis the diseased media yields to the force of the blood pressure either generally or at its weakest point resulting in a fusiform or sacculated aneurysm, in pulmonary hypertension due to Bilharzia the vessel wall yields to the force of the raised pressure in spite of a hypertrophied healthy media. This may be due to the fact that unlike the systemic arteries the pulmonary vessels are not meant to stand a markedly raised pressure.

The two cases here described illustrate two stages in the pathology of bilharzial cor pulmonale. The first case is one in which the heart was under the strain of a moderately raised pulmonary pressure and, had the patient survived the repeated hematemesis, it is possible that he may have lived a few more years. The second case, on the other hand, is that of a man in whom the pathologic process was advanced so as to produce cardiac strain with subsequent failure which incidentally was the cause of his death. It is thus evident that the condition can be progressive or stationary depending upon whether the infection remains or is terminated by treatment, and the cardiac state produced also depends upon how far the arteriolar changes have progressed before treatment was secured. The survival period for these patients depends mainly upon the height of pressure in the pulmonary circulation. With a mild or moderate rise of pressure the patients, though they may be incapacitated for heavy work, usually survive for several years. A marked rise of pressure on the other hand ultimately leads to failure, and compensation though it may be secured through recognized methods of treatment is not usually long lasting.

Our first case showed a partial right bundle branch block in the electrocardiogram, a change which though common in the clinically similar condition of atrial septal defect is rather uncommon in bilharzial pulmonary hypertension.

We are indebted to Dr. Ramley for the results of the cardiac catheterization.

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CHRONIC CONSTRICTIVE PERICARDITIS AND RHEUMATIC HEART DISEASE

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CHRONIC constrictive pericarditis is a well-established clinical entity which is often amenable to surgical treatment. Its etiology is frequently obscure and its manifestations confusing. While the diagnosis of this condition may be quite simple in the presence of the classical findings. many cases are improperly diagnosed as tuberculous peritonitis, portal cirrhosis of the liver, valvular heart disease, or ascites of unknown origin.[1] Confusion arises especially when the heart is not small, the sounds are not quiet, and the pulsations not appreciably diminished. When constrictive pericarditis is associated with other forms of heart disease, the disease may be readily overlooked. Since constrictive pericarditis is a surgically remediable condition, the importance of its recognition is apparent. A proper awareness of the less typical aspects of this condition will result in the discovery of many more cases.

In our experience one of the most difficult diagnostic problems has been the coexistence of constrictive pericarditis and rheumatic heart disease. In a series of eighteen cases of constrictive pericarditis at the Veterans Administration Hospital, Bronx, N. Y., all proved by operation or autopsy, there were five with rheumatic heart disease. Three additional patients (of the eighteen) had a history of recurrent rheumatic fever but no objective evidence of valvular heart disease. Of the remaining ten patients, two were due to tuberculosis, one secondary to a foreign body,[2] and the others were of unknown etiology. The five cases associated with rheumatic heart disease will be reported in detail.

CASE REPORTS

CASE 1.—A 41-year-old Negro man was admitted on March 7, 1945, with complaints of swelling of the legs, dyspnea, and weakness. Previously, in November, 1944, he had been admitted to another hospital acutely ill with fever and chest pain. Blood cultures were positive for a pneumococcus and he developed a frank pericarditis with effusion. Clinical improvement was noted with the administration of penicillin and sulfadiazine and blood cultures became sterile. He left that hospital in February, 1945, and while at home developed edema of the legs and ankles, dyspnea, and weakness for which he was admitted to the Bronx Veterans Administration Hospital.

There was a history of recurrent polyarthritis since the age of 16, but the patient denied any knowledge of rheumatic fever or heart disease.

Initial examination revealed a well-developed, well-nourished Negro who appeared acutely and chronically ill. Dullness was present at both lung bases and fine moist râles were heard on the right side posteriorly. The heart was enlarged to the left. There were presystolic and systolic

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murmurs at the apex and a blowing diastolic murmur at the aortic area. The rhythm was regular, rate 80; the pulse was collapsing in character. Blood pressure was 126/56 mm. Hg. The liver was enlarged six fingerbreadths below the right costal margin and was tender. The spleen was not palpable. Ascites was not present. Two plus pitting edema was noted in both ankles and legs.

The chest roentgenogram indicated transverse enlargement of the heart with straightening of the left border (Fig. 1). On fluoroscopy the heart pulsations were within normal limits. The electrocardiogram showed low voltage of all QRS complexes, with low amplitude and diphasic T waves throughout.

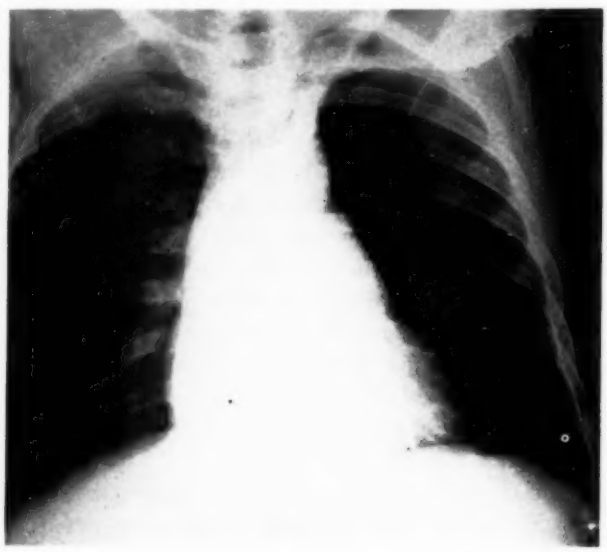

Fig. 1 (Case 1).—Angiocardiogram revealing thickening of pericardium, cardiac enlargement, and straightening of left cardiac border. (Medical Illustration Laboratory, Veterans Administration Hospital, Bronx, N. Y. Neg. No. 81-8165 b.)

Despite prolonged treatment with rest, digitalis, and mercurial diuretics there was progression in his congestive heart failure, with increasing peripheral and pulmonary edema and the appearance of ascites. Abdominal paracenteses were done every ten to fourteen days, and each time from 6 to 12 liters of fluid were removed. The venous pressure was 294 mm. of water; the arm-to-tongue circulation time was 22 seconds; the arm-to-lung circulation time was 17 seconds.

It was suspected that chronic constrictive pericarditis was present in addition to the rheumatic heart disease and on Feb. 28, 1947, a thoracotomy was done. At operation the pericardium was markedly thickened and fibrotic, causing constriction throughout. Pericardiectomy was performed. Microscopically no specific etiology could be established.

Postoperatively there was marked improvement. Dyspnea disappeared and all signs of congestive heart failure, including the ascites, gradually cleared. After five months the venous pressure was down to 100 mm. of water, and the arm-to-tongue circulation time was 16 seconds.

The patient has been examined at regular intervals since and has remained well. In April, 1952, five years after his operation, he was entirely free of congestive heart failure. No specific cardiac medication had been given during this period. The heart was still enlarged and the murmurs of mitral insufficiency, mitral stenosis, and aortic insufficiency were still present and unchanged. The rhythm remained regular (Fig. 2).

CASE 2.—A 38-year-old Cuban man was admitted on March 22, 1951, because of increasing signs of congestive heart failure. There was a history of frequent tonsillitis since childhood, but of no polyarthritis or recognized rheumatic fever.

After several episodes of pneumonia in 1945 he developed easy fatigability, vague aches in chest, head and legs, and exertional dyspnea. During hospitalization at that time the heart sounds were described as of poor quality, but no murmurs were heard. Enlargement of the left atrium was seen fluoroscopically and the electrocardiogram showed inverted T waves in the standard leads. The liver was palpable one fingerbreadth below the right costal margin.

Two years later during hospitalization for an acute undiagnosed febrile illness, an aortic diastolic murmur was heard. The liver was five fingerbreadths below the right costal margin and the spleen two fingerbreadths below the left. The chest roentgenogram was reported to be normal. The antistreptolysin titer was 712 units per cubic centimeter.

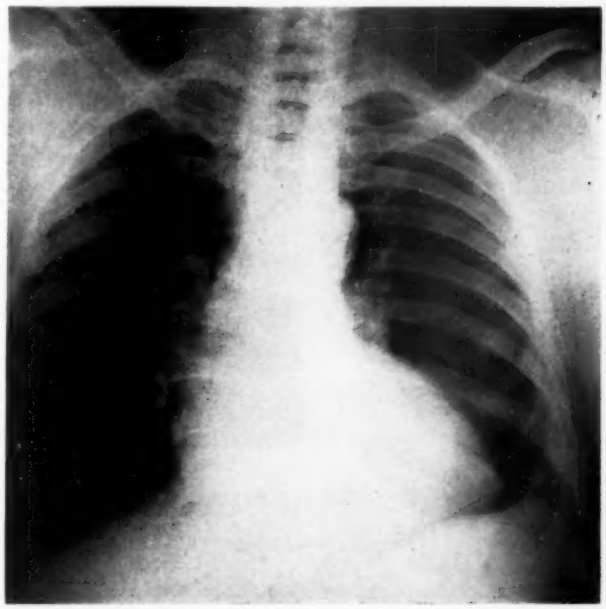

Fig. 2 (Case 1).—Roentgenogram of heart five years later disclosing cardiac enlargement of left ventricular type. (Medical Illustration Laboratory, Veterans Administration Hospital, Bronx, N. Y. Neg. No. 81-8165 a.)

In 1948 a definite diagnosis of rheumatic heart disease with mitral insufficiency, mitral stenosis, and aortic insufficiency was made. The venous pressure measured 210 mm. of citrate solution. Because of neck vein distention, hepatosplenomegaly, and ankle edema he was digitalized and put on a low-salt diet. He was followed for two years on this regimen and during this time the liver and spleen remained palpable, the ankle edema was intermittent. Repeated complete blood counts and erythrocyte sedimentation rates were normal. In January, 1951, a left pleural effusion was noted, and because of the increase in fluid accumulation the patient was admitted to the Bronx Veterans Administration Hospital on March 22, 1951.

On examination the patient was chronically ill and slightly orthopneic. Mild distention of neck veins was noted. There were signs of left pleural effusion, but the right lung was clear. Examination of the heart revealed the point of maximum intensity of the apical impulse to be just outside the midclavicular line in the fifth intercostal space. The heart sounds were of fair quality with A_2 being equal to P_2. The first apical sound was not accentuated. No thrill was palpated. There was a soft low-pitched systolic murmur and a low-pitched rumbling diastolic murmur at the apex. A loud, high-pitched aortic diastolic murmur was transmitted downward along the left sternal border. There was normal sinus rhythm at a rate of 84. The blood pressure was 120/70 mm. Hg. No Broadbent's sign was evident. The liver was five fingerbreadths below the

right costal margin and the spleen one fingerbreadth below the left. Both organs were slightly tender. No ascites, edema, or clubbing were present.

The patient was given a low-salt diet and maintenance digitalis. Attempts at further diuresis with mercurials were unsuccessful. His weight remained stationary; the temperature range was normal. The hepatosplenomegaly persisted, and ankle edema was intermittent. Ascites did not appear. Thoracocentesis was done on several occasions and was followed by rapid reaccumulation of fluid. Venous pressure varied between 170 and 195 mm. of citrate solution. The arm-to-tongue circulation time was 23 to 30 seconds; the arm-to-lung time was 9 seconds. The electrocardiogram showed low voltage of QRS and T waves, with little change on serial tracings (Fig. 3). Pericardiectomy over the left side of the heart was performed with the removal of thickened fibrotic pericardium which, on microscopic examination, showed nonspecific inflammatory changes. Cardiac standstill occurred during operation and after massage of the heart normal rhythm returned. Because of this complication the operation was not extended to include resection of the constricted pericardium of the right side. Postoperatively, auricular fibrillation developed but reverted to normal sinus rhythm when the patient was redigitalized.

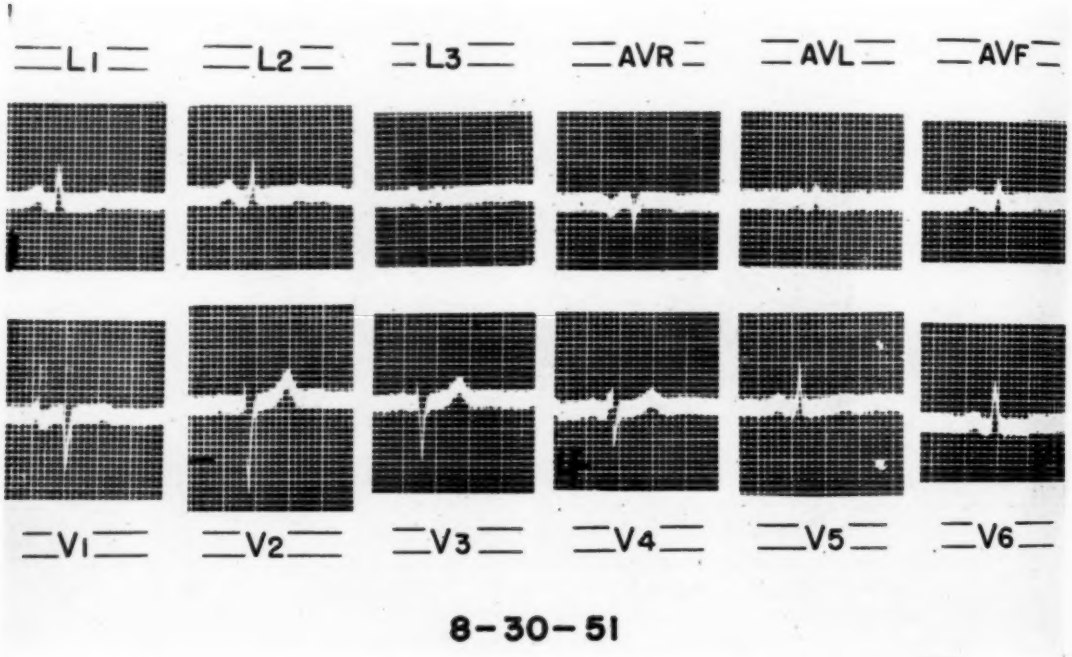

Fig. 3 (Case 2).—Electrocardiogram with low voltage QRS and T waves. (Medical Illustration Laboratory, Veterans Administration Hospital, Bronx, N. Y. Neg. No. 81-8163 b.)

There was gradual clinical improvement. In February, 1952, the venous pressure measured 70 mm. Pleural effusion did not reaccumulate but the liver remained palpable three fingerbreadths and the spleen one fingerbreadth below the costal margins. Mild transient ankle edema was noted.

The patient was discharged from the hospital on March 2, 1952, and continued to take Digoxin 0.5 mg. daily. He was readmitted on March 18, 1952, because of recurrence of auricular fibrillation. Normal sinus rhythm was restored with quinidine and he was again discharged on April 2, 1952, taking both Digoxin and quinidine (Fig. 4). Further operative intervention will depend on the future course of the patient.

CASE 3.—A 29-year-old white man in 1940, at the age of 18 years, developed rheumatic polyarthritis and carditis necessitating hospitalization for eight months. Following this he remained apparently well except for slight exertional dyspnea until 1949 when he became dyspneic even at rest. Gradual swelling of the abdomen and ankle edema started at that time. Orthopnea ensued, and dyspnea became severe despite digitalization.

The patient was admitted to the Bronx Veterans Administration Hospital on March 21, 1950, with neck vein distention, right pleural effusion, and bilateral basal pulmonary râles. The point of maximum intensity of the cardiac impulse was in the sixth intercostal space in the anterior axillary line. P_2 was louder than A_2, and M_1 was accentuated. There were both systolic and diastolic murmurs at the apex and an aortic diastolic murmur. Auricular fibrillation was present with a ventricular rate of 100. Blood pressure was 140/60 mm. Hg. Massive hepatomegaly, 2 plus dependent edema, and marked ascites were evident.

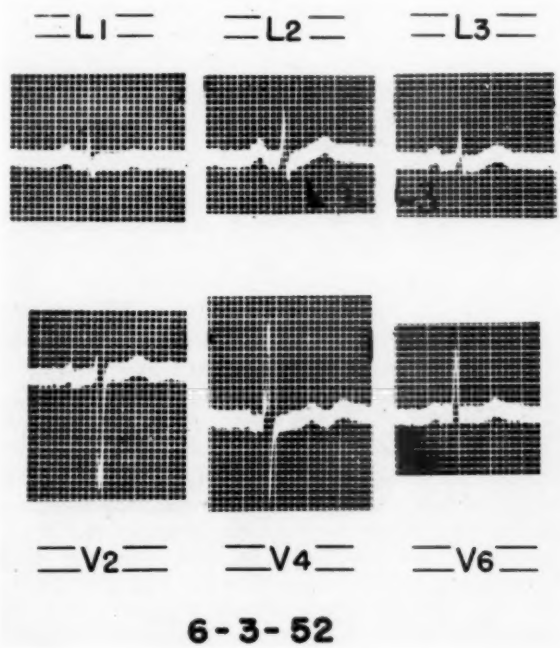

Fig. 4 (Case 2).—Electrocardiogram nine months postoperative. QRS and T waves show increased voltage. (Medical Illustration Laboratory, Veterans Administration Hospital, Bronx, N. Y. Neg. No. 81-8163 a.)

The electrocardiogram showed nonspecific T-wave changes. Chest roentgenograms revealed a right pleural effusion, hilar engorgement, and generalized cardiac enlargement without evidence of pericardial effusion or calcification.

A prolonged course of refractory and intractable congestive heart failure ensued, despite low-sodium diet, digitalis, mercurial diuretics, paracenteses, and other supportive measures, and the patient expired on June 5, 1951.

Autopsy revealed rheumatic aortic and mitral valvulitis, marked cardiac hypertrophy (heart weighed 800 grams), and calcifying pericarditis of unknown etiology. The pericardium was totally adherent to the epicardium and was thickened, fibrotic, and filled with areas of calcification.

CASE 4.—A 71-year-old white man was admitted with a history of rheumatism with swollen joints at the age of 5 years, and with recurrent attacks until the age of 19. He had no knowledge of murmurs or the presence of heart disease.

There was a twelve-year history of exertional dyspnea progressing to dyspnea at rest prior to admission to the Bronx Veterans Administration Hospital on Nov. 14, 1950. At the time of his hospitalization there was neck vein distention and bilateral basal pulmonary râles. The heart was generally enlarged, P_2 louder than A_2, and auricular fibrillation was noted. There was a systolic murmur at the apex but no diastolic murmurs. Blood pressure was 140/80 mm. Hg. The liver was enlarged to four fingerbreadths below the costal margin and there was 4 plus edema of the lower extremities. The electrocardiogram demonstrated low and diphasic T waves in standard and precordial leads.

There was good response to digitalization. No signs of congestive heart failure except for moderate hepatomegaly remained at the time of his discharge on Jan. 12, 1951. Venous pressure was 120 mm. of citrate solution, and arm-to-tongue circulation time was 15 seconds.

The patient was readmitted to the hospital on Feb. 24, 1951, because of dyspnea, orthopnea, cough, and fever of 103° F. Râles were present over the right lower lobe without signs of consolidation, and a chest roentgenogram established the presence of pneumonia in that area. The recurrence of his congestive heart failure was ascribed to the pneumonia and to the patient's negligence in taking his digitalis. The pneumonia responded readily to penicillin and the heart failure cleared when he was redigitalized. At this time the auricular fibrillation reverted to normal sinus rhythm. The electrocardiogram showed inverted T waves over the entire precordium. He was about ready for discharge when he died suddenly.

Autopsy revealed rheumatic mitral and aortic valvulitis, coronary atheromatosis, and myocardial fibrosis but no recent coronary occlusion or myocardial infarction. The pericardium was thickened, fibrotic, and completely adherent to the epicardium. It was constrictive in character and nonspecific in etiology.

CASE 5.—A 58-year-old man was admitted to the Bronx Veterans Administration Hospital on Sept. 28, 1950, because of dyspnea and ankle edema. There was a history of diabetes for five years but no knowledge of rheumatic fever. Dyspnea first appeared three years prior to admission. Two years later when this became severe and was accompanied by ankle edema, the patient was digitalized. At first there was good response to treatment but gradually the congestive heart failure became refractory to mercurial diuretics and the patient was hospitalized.

On admission he was cyanotic and dyspneic. Distended neck veins filled from below. There were râles at both lung bases and pleural effusion on the right. The point of maximum intensity of the apical impulse was in the sixth intercostal space in the anterior axillary line, A_2 was louder than P_2, and both systolic and diastolic murmurs were heard at the apex and at the base of the heart. There was a regular rhythm at a rate of 92. Blood pressure was 150/50 to 0 mm. Hg. The liver was palpable four fingerbreadths below the costal margin; there was no ascites. Four plus edema of the lower extremities and genitalia was present. The electrocardiogram showed low or inverted T waves in the standard leads. Chest roentgenogram revealed generalized cardiac enlargement and signs of congestive heart failure. Serologic tests for syphilis were positive despite the patient's denial of clinical syphilis. The response to digitalis, mercurial diuretics, and supportive measures was poor; the patient's rapid downhill course ended on Oct. 6, 1950.

Autopsy revealed rheumatic and arteriosclerotic aortic valvulitis and no evidence of syphilitic heart disease. The pericardium was thickened and totally adherent to the epicardium. There was constriction but no calcification. No specific etiology of the pericarditis could be ascertained after microscopic examination.

Three other patients with calcifying and chronic constrictive pericarditis gave a history of recurrent polyarthritis but no objective valvular heart disease was evident. Two of these patients had successful pericardiectomies. The other was not submitted to operation, the diagnosis being established at autopsy.

The remaining ten patients with constrictive pericarditis all had operations performed. Results were good in six, no definite improvement in one, and early postoperative death in two. Deaths were due to pulmonary embolus in one, and pneumonia in the other.

Original impressions ran a gamut from the true diagnosis to valvular heart disease alone, and included several suspected diagnoses of cirrhosis. The etiology of the pericarditis was established in only three of the eighteen cases. Two were tuberculous and one was secondary to a foreign body. Although a history of severe pneumonias was obtained from four patients, no specific microscopic diagnosis could be established in the remaining fourteen cases. The role of rheumatic fever in the etiology is still an open question and we have been impressed in this series not by a causal relationship but by a coexisting one.

DISCUSSION

In a series of sixty-one cases of constrictive pericarditis ten had a past history of rheumatic fever.[3] In only one could this have been an etiologic factor, and the authors thought it coincidental. Harrington[4] found an even smaller incidence of rheumatic disease. Only one of his patients had a rheumatic history and in this patient the pericarditis was proved tuberculous.[5] Others report similar findings.[6-8]

In 6,100 routine autopsies Sprague and associates[9] found only six cases of adherent pericardium without valvular disease in patients with a rheumatic history. None of these had evidence of Pick's disease. Mortensen and Warburg[7] felt that the earlier view that rheumatic fever was frequent in this disease was due to the lack of distinction made between pericarditis in general and the constrictive forms. They presented the view that a history of rheumatic fever makes the diagnosis of constrictive pericarditis doubtful. Harrison and White[8] mentioned a follow-up of 1,500 cases of rheumatic fever at the House of the Good Samaritan in Boston by Dr. E. F. Bland which revealed no cases of chronic constrictive pericarditis.

The classical signs and symptoms of constrictive pericarditis: dyspnea, ascites, edema, elevated venous pressure, together with low voltage and primary T-wave changes in the electrocardiogram, have recently been adequately reviewed.[3]

There is a prevailing impression that the heart in constrictive pericarditis is small and quiet. Our own experience with this disease suggests that the size of the heart and loudness of the heart sounds should play no role in exclusion of the diagnosis of constriction. It should also be emphasized that the amplitude of cardiac pulsations may be within normal limits in the presence of this disease.

It has been suggested[6] that the absence of other types of heart disease is a valuable clue in arriving at a diagnosis of constrictive pericarditis. The evidence submitted in this study should serve to emphasize that the converse is not true and that constrictive pericarditis may well accompany other forms of heart disease. If this fact is borne in mind, more cases of this surgically remediable condition will be discovered.

Although we cannot implicate rheumatic disease as an etiologic factor, our experience has indicated that in the patient with valvular heart disease constrictive pericarditis can and does occur. It is this group of patients who easily can be overlooked and in whom the diagnosis and treatment is so important.

Examples in point are Cases 1 and 2 in this report. It is questionable whether the course of the disease in the third case could have been altered if constriction had been suspected before death. We have become aware of the fact that, in any patient with heart disease and an atypical course, it is well to suspect constrictive pericarditis. The investigation often must be quite intensive before it is excluded or proved. Angiocardiography may be helpful in demonstrating a thickened pericardium. The decision as to whether constriction is present, or if operation is necessary, must be resolved by astute clinical judgment. The presence of definite rheumatic heart disease does not preclude the existence of a superimposed chronic constrictive pericarditis.

In arriving at the diagnosis, the question of heart size has little bearing as the heart may be small, normal, or large. It is also emphasized that cardiac pulsation on fluoroscopy may be normal or only slightly decreased despite significant constriction of the heart. If the question of constriction is still unresolved following thorough study, recourse should be had to exploratory thoracotomy. This procedure now carries little risk and the benefit to the patient may be very great.

SUMMARY

1. In a series of eighteen cases of chronic constrictive pericarditis, five had coexisting rheumatic valvular disease and are reported in detail.

2. If constrictive pericarditis is suspected in patients with heart disease who have an atypical course, more cases will be discovered.

3. Cardiac enlargement, normal intensity of heart sounds, and normal cardiac pulsations are not rare in patients with constrictive pericarditis.

4. The presence of definite rheumatic heart disease does not exclude the existence of associated chronic constrictive pericarditis although there is no evidence that the two conditions are causally related.

5. It is of significance that in three of the five cases in which constrictive pericarditis was associated with rheumatic heart disease, there was a history of another etiologic factor which may have played a role in the development of the disease.

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RUPTURED INTERVENTRICULAR SEPTUM AND RUPTURED PAPILLARY MUSCLE IN TWO CASES OF ACUTE CORONARY ARTERY DISEASE

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IN THIS report are described two cases of myocardial infarction, one with rupture of interventricular septum and one with rupture of the posterior papillary muscle. The newly developed systolic murmur which appeared in each instance led to the clinical recognition of these conditions. The site of maximum loudness of the murmur was the dominant element in the differential diagnosis between rupture of the septum and of the papillary muscle. In a review of the literature[1-4] we found that rupture of the interventricular septum was recognized ante mortem in fifteen of fifty-six cases. A case with clinical diagnosis of ruptured papillary muscle which was confirmed at autopsy was first reported by Davison.[5] A second case was reported by Schwartz and Canelli[3] and the present case is the third. However, it is likely that rupture of a papillary muscle, though a rare complication of acute coronary artery disease, occurs more often than the few reported instances would suggest.

CASE REPORTS

CASE 1 (M.S. 87396).—A 70-year-old woman was admitted to the Jewish General Hospital on Oct. 7, 1951. Since 1936 she had had cardiac pain on walking, which was relieved by rest; the blood pressure was sometimes high but usually normal. At midnight on the day of admission she suddenly experienced severe retrosternal pain with radiation through to the back and down both arms. The pain persisted for about five hours in spite of a hyperdermic injection of morphine sulfate administered by her physician. She was admitted to the hospital approximately fifteen hours after the onset of the pain. She was pale and weak; pulse was 88, regular and of a good quality, blood pressure was 180 mm. Hg systolic, and 95 mm. Hg diastolic, and temperature 99.4° F. rectally; respirations 26. Hemoglobin was 12.4 Gm., white blood count 14,500, and sedimentation rate 25 mm. per hour. Serial electrocardiograms showed typical signs of an anteroseptal infarct with extension to the diaphragmatic aspect of the heart. Strict bed rest was prescribed. Anticoagulant therapy (Dicumarol) was given. During the first few days in the hospital the patient gained in strength and was comfortable; the blood pressure was within normal limits. On Oct. 12, our colleague, Dr. J. Wener, was the first to hear new features of the systolic murmur which he described as follows: "There is a louder systolic murmur than was heard on admission." The next day he noted the murmur was, " . . . loud, blowing and loudest at the fourth and fifth left intercostal spaces near the nipple line. This murmur now occupies the whole first sound. . . . ruptured interventricular septum must be considered." A few minutes later H.N.S. described the

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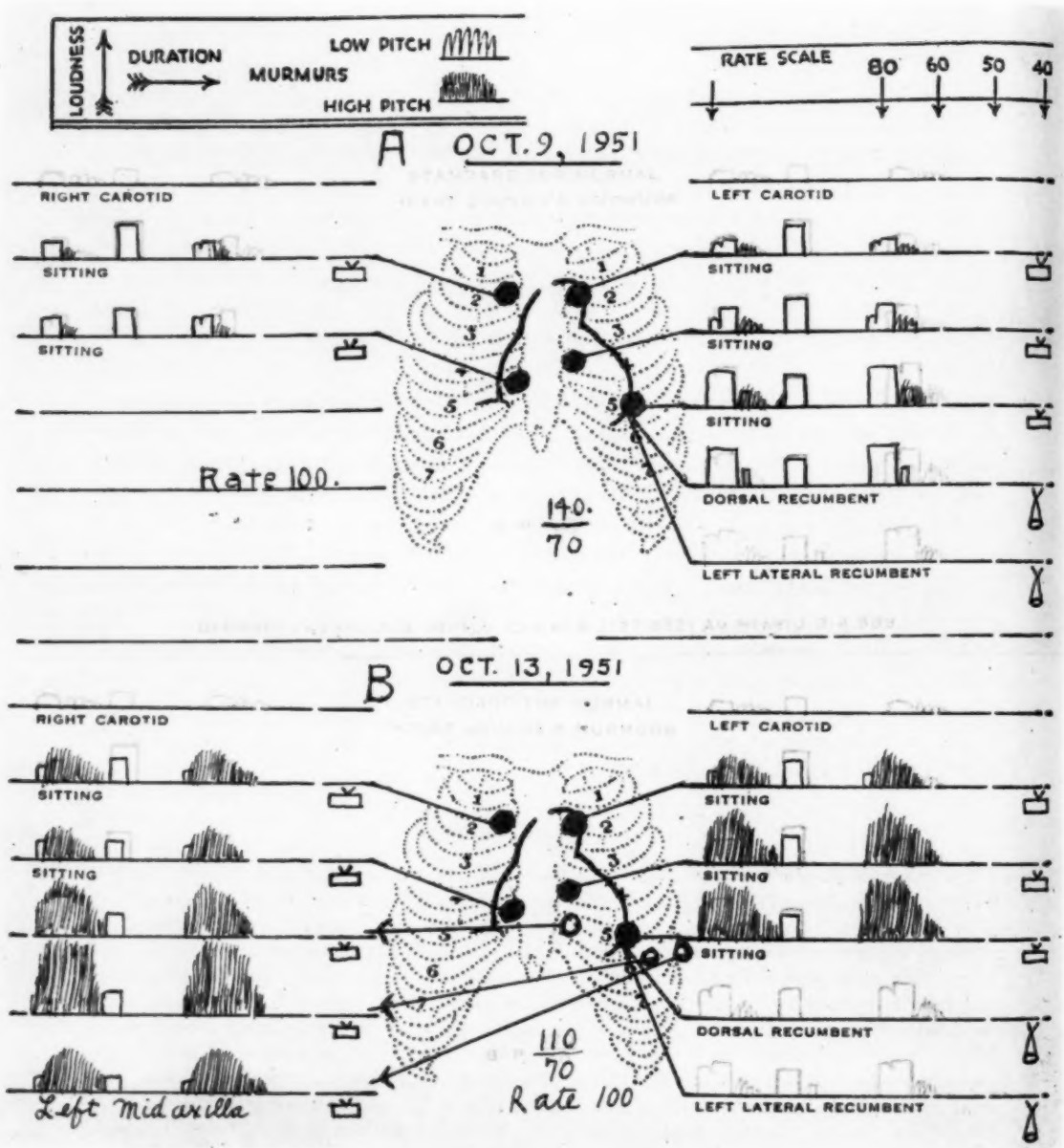

Fig. 1 (Case 1). —A, Heart sounds and murmurs described by quantitative symbols* on the third day of illness with acute anteroseptal ventricular myocardial infarct. The first sound shows right split

(For remainder of legend see opposite page.)

*This method of describing heart sounds and murmurs by quantitative symbols was devised by H.N.S. in 1926 and described in 1932[7] and 1933.[8] In 1948, a chart was devised on which the modal pattern of normal sounds and murmurs is printed as a standard guide in writing the symbols for the sounds and murmurs of the patient being examined. These illustrations exemplify the use of this chart. The sounds are represented by rectangles; the ordinate of the symbol indicates loudness and the abscissa duration; coarse murmurs are drawn as waves of rather widely separated lines and blowing murmurs as more closely packed vertical lines; vertical length indicates loudness; the horizontal space occupied by the symbol shows the time relations of the murmur to the heart sounds. An arbitrary scale guides in representing heart rate; the faintly printed symbols of the normal pattern are designed for the rate of 80 per minute.

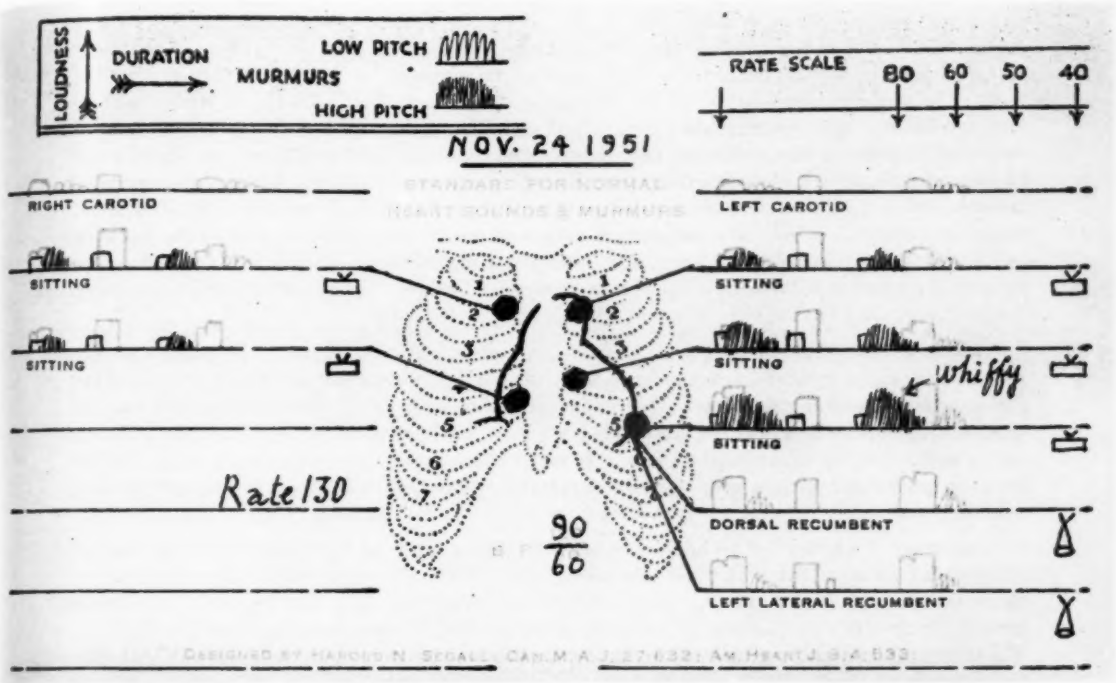

Fig. 2 (Case 2). —Heart sounds and murmurs described on the third day of illness. Both sounds are faint: this is to be associated with the low blood pressure related to the state of shock. The blowing systolic murmur had a high-pitched "whiffy" quality: it was loudest and longest at the apex and was louder along the left than along the right border of the sternum; it was least loud near the fifth right intercostal space. This murmur was interpreted as evidence of ruptured posterior papillary muscle of left ventricle.

(*Continuation of legend from opposite page.*)

at the apex and "normal" type of left split along left border of sternum: the "right split" suggests ventricular asynchronism with left ventricular contraction preceding right. The short early systolic murmur is of physiologic type. The second sound is within the range of normal.

B, Heart sounds and murmurs described by symbols on the seventh day of illness. The loud, blowing systolic murmur masks the first sound at and near the apex and along the left border of the sternum; a trace of the beginning of the first sound is shown along the right border of the sternum. The murmur is loudest and longest in the sixth left intercostal space just to the left of the midclavicular line and is least loud and shortest at the right border of the sternum near the fourth intercostal space; the murmur is well heard in the left midaxillary line near the sixth intercostal space. It is only a little less loud at the fourth left intercostal space near the sternum than at and near the apex. The second sound is everywhere less loud and shorter than three days previously; this is to be associated with lower pulse pressure. The murmur was interpreted as representing perforation of interventricular septum near the apex.

sounds and murmurs using symbols (Fig. 1, *A*). At first he considered ruptured papillary muscle as more likely, but in the course of bedside discussion he suggested that the signs could represent perforation of the septum close to the apex, because the murmur was loudest in this region (Fig. 2, *B*). The murmur persisted during the remaining eleven days of life. On the seventh day of illness, she became very apprehensive, complained of feeling generally unwell, but had no pain or shortness of breath. The pulse was 110, the blood pressure dropped to 80 mm. Hg systolic and 70 mm. Hg diastolic. Electrocardiograms showed no significant change; tachycardia persisted between 110 and 120, and the blood pressure ranged from 110 mm. Hg systolic and 80 mm. Hg diastolic to 80/70. A few moist inspiratory râles were heard over the lower lobe of the left lung on Oct. 20, 1951. In spite of mercurial diuretics and digitalization, the patient's condition deteriorated gradually without development of congestive failure. She expired on the seventeenth hospital day, after having been in a state of shock for seven hours.

Clinical Interpretation.—Clinical and electrocardiographic evidence indicated that this patient had acute coronary artery disease with ventricular myocardial infarction that involved the anteroseptal and apical regions. On the sixth day of illness a newly developed systolic murmur was heard; it was loudest near the apex and only a little less loud at the left border of the sternum, near the fifth and fourth intercostal spaces. It was interpreted as representing perforation through the interventricular septum near the apex; ruptured anterior papillary muscle was considered a less likely possibility because the murmur was so loud near the sternum.

Anatomic Pathology.—The heart weighed 440 grams with enlargement mainly of the left ventricle which was dilated and had thickened walls. The right ventricle was dilated. The anterior wall was markedly thinned commencing 4 cm. above the apex and extending downward around the apex to involve about 1 cm. of the posterior wall, in some places measuring only 3 mm. The myocardium in this region was soft, flabby, and showed scattered grayish areas which were for the most part subendocardial. The apical half of septum was extremely thin and formed a distinct aneurysm, bulging into the cavity of the right ventricle. When held up to the light the apical portion of the septum was seen to be translucent in several places near the junction of the anterior wall with the septum. At a point about 1 cm. above the apex there was a slitlike perforation about 0.5 cm. long, hidden from immediate view by the calumnae carneae. The coronary arteries showed extensive arteriosclerosis with irregular areas of calcification and stenosis. The most extreme stenosis was noticed in the anterior descending ramus of the left coronary artery at a point 7 cm. from its origin. There was no thrombotic occlusion. Microscopic section of the interventricular septum revealed changes which were interpreted as being compatible with myocardial infarction of two weeks' duration.

CASE 2 (F.S. 88363).—A 51-year-old white man was admitted to the Jewish General Hospital on Nov. 22, 1951, with the diagnosis of acute coronary artery disease. He had been in good health until midnight on Nov. 18, 1951, when he experienced a burning, retrosternal pain which persisted all night. He returned to his usual work (sausage maker) the next day and continued working without discomfort until three days later when he had a recurrence of the pain accompanied by extreme shortness of breath and profuse perspiration. This led to his admission to hospital. He was in acute respiratory distress, sweating profusely, pulse 120 and regular, respiration 28, blood pressure 84 mm. Hg systolic and 70 mm. Hg diastolic, and temperature 100.4° F. rectally. There were some fine inspiratory râles of pulmonary edema at both bases. The heart sounds were distant and no adventitious sounds were noticed. The abdomen was soft with no areas of tenderness or palpable masses. An electrocardiogram, recorded soon after admission, showed sinus tachycardia, deep Q waves, elevated S-T segments, negative T waves in Leads II, III, and aV_F consistent with a recent posterior wall ventricular infarct. The hemoglobin was 14.35 Gm., white blood count 15,000 and sedimentation rate 11 mm. per hour. The patient was placed in an oxygen tent, given Demerol Hydrochloride, anticoagulants (heparin and Dicumarol) and was digitalized. Because of his shocklike state and hypotension, he was given ephedrine, ¾ grain subcutaneously every three hours; this seemed to raise the blood pressure to 100 mm. Hg systolic and 80 diastolic. There was no appreciable improvement: the temperature rose to 105° F. rectally on the evening of Nov. 24; the tachycardia, rate 120, and dyspnea persisted. On the second hospital day, Nov. 23, a moderately loud blowing systolic murmur, loudest at the apex, was heard. (Fig. 2.) His private

physician, Dr. S. Barskey, informed us that he had found the heart sounds normal, without murmurs, on several occasions in the past three years. The blood pressure remained at 95 to 85 mm. Hg systolic and 70 mm. Hg diastolic in spite of ephedrine therapy; the shocklike state persisted and the patient expired on the fourth hospital day.

Clinical Interpretation.—The clinical evidence indicated that there was infarction of the posterior ventricular wall. The newly developed systolic murmur, loudest at the apex, was interpreted as evidence of a ruptured papillary muscle, and it was predicted that the posterior papillary muscle was involved because of the site of the infarct. As the murmur was loudest at the apex, it was considered unlikely that it might be due to perforation of the interventricular septum.

Anatomic Pathology.—The visceral surface of the pericardium showed scattered areas of hyperemia and petechiae with small fibrinous adhesions. Over the posterior aspect of the ventricular surface the two layers of the pericardium were loosely bound by easily separable fibrinous adhesions. The heart weighed 350 grams. The right side of the heart was not unusual. On section through the posterior wall of the left ventricle, behind the base of the posterior papillary muscle, the myocardium was found to be slightly softer than usual, and the cut surfaces showed irregular, pale yellow and brown areas within the wall. The wall in this situation was slightly thinned; the posterior papillary muscle, 4 mm. from its insertion into the ventricular wall, showed a partial rupture which involved approximately one-half the thickness of the muscle. The remaining one-half of the papillary muscle was intact. The two surfaces at the site of rupture of the muscle were quite ragged and hyperemic. The cut surfaces of the posterior papillary muscle were mottled yellow and gray. These changes were similar to and continuous with the changes in the infarcted posterior wall of the left ventricle. The coronary arteries showed a right preponderant distribution with the left circumflex coronary artery ending on the obtuse margin of the heart and the right coronary artery crossing the midline posteriorly. On being opened they showed moderate arteriosclerotic changes and in the right coronary artery, at a point 13 cm. from its origin, just before it gave off its posterior descending ramus, there was a small reddish-brown thrombus attached to the wall of the vessel. No other thrombi, emboli, or areas of complete occlusion were encountered at any point. Microscopic sections of the myocardium taken through the posterior wall to include the base of the posterior papillary muscle, revealed typical morphology of a recent myocardial infarct. The lungs were edematous.

DISCUSSION

In the first case the possibility of ruptured papillary muscle could not be excluded for the murmur was somewhat louder at the apex than at the left border of the sternum; but perforation of the interventricular septum, situated near the cardiac apex, was considered more likely because the murmur was almost equally loud at both these areas of auscultation. The autopsy revealed a slitlike septal perforation about 1 cm. above the apex. It is noteworthy that the systolic murmur was everywhere high pitched and blowing in quality. This may be explained by the shape of the perforation which must have made for an almost linear opening during ventricular systole. Eddies produced under these physical conditions would be similar to those created in the case of a slight degree of valvular insufficiency. The left-to-right shunt in this case must have been too small to have any significant effect on cardiac dynamics. This is supported by the fact that the patient did not develop congestive cardiac failure, although she lived for eleven days after the murmur appeared. She died in shock which began seven hours before death. The patient mentioned by Wood and Livezey[9] lived for almost five years after the appearance of the murmur of ruptured interventricular septum; congestive cardiac failure which developed early in the illness was treated with mercurial diuretics; at autopsy the perforation was large, 1.5 cm. in

diameter. The mechanical disturbance of cardiac function resulting from the small perforation in our case must have been much less than from a large opening in the septum. It is doubtful whether it played a significant role in causing the patient's death by virtue of the right-to-left shunt.

In the second case the murmur was more high pitched than in the first and was described as "whiffy." As the tear in the posterior papillary muscle involved only one-half its thickness, the degree of mitral regurgitation must have been small through a rather narrow slitlike orifice between the edges of mitral valve cusps. The mechanical disturbance in cardiac function was probably too little to affect the course of the illness. The patient died in shock which appeared soon after the onset of acute coronary artery disease. There was clinical evidence of pulmonary edema before the murmur appeared and it increased in degree and extent in the course of the three days until death occurred.

The mechanism of rupture of the heart is not yet clearly understood. One of us (H.N.S.) in discussing myocardial rupture of the ventricular wall[6] postulated that it occurs when usual interruption of continuity of muscle fibers in an infarct happens to involve a line of cleavage which readily leads to extension; thus myocardial rupture takes place even with the low systolic pressure during shock. In these two cases, no acute event such as physical exertion occurred, which could be blamed for the cardiac rupture. The first patient was being treated with absolute bed rest and the blood pressure was within the range of normal. The second patient was under the influence of sedatives and continuously in bed, in an oxygen tent almost from the beginning of the illness. The blood pressure was low. These observations tend to confirm the view that rupture of any part of the myocardium is apt to be independent of such elements as physical exertion. This has encouraged us to beware of being frightened by the possibility of cardiac rupture in cases of acute coronary artery disease. The fitness of the patient to go to the bathroom rather than use a bedpan and to sit in a chair during the day instead of remaining too long on a regimen of absolute bed rest must be estimated without being dominated by fear of cardiac rupture which cannot be prevented by any known measures, not even by the most rigid program of absolute bed rest. Because of the statistically significant fact that cardiac rupture usually occurs within the first two weeks after the onset of acute coronary artery disease, conservative management of the illness would call for absolute bed rest during the first fortnight.

SUMMARY

1. In one case of acute coronary disease with evidence of anteroseptal ventricular myocardial infarct, the clinical diagnosis of perforation of the septum near the apex was made and confirmed at autopsy. The newly developed systolic murmur was loud both at the apex and near the fifth and fourth intercostal spaces and was high pitched.

2. In the second case, rupture of the posterior papillary muscle was diagnosed clinically because the electrocardiograms indicated posterior ventricular wall infarction and the newly developed systolic murmur was loudest at the apex. At autopsy, the posterior papillary muscle was found torn through half its thickness.

3. In both cases rupture of myocardium occurred during a regimen of absolute bed rest unrelated to any physical exertion. This may be added to the sum of experience which suggests that there is no cause-and-effect relationship between physical exertion and myocardial rupture.

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THE ELECTROCARDIOGRAM AND POTASSIUM METABOLISM DURING ADMINISTRATION OF ACTH, CORTISONE, AND DESOXYCORTICOSTERONE ACETATE

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CERTAIN characteristic electrocardiographic changes have been observed in many cases with abnormally low plasma potassium levels: an increase in the Q-T intervals, a depression of the S-T segments, a broadening, lowering, or inversion of the T waves, and prominent U waves.[2-4,6-8,13,16,17,19] Bellet and associates[3] found ". . . that the Q-T interval prolongation was a crude guide of the degree of hypopotassemia." In their cases the mean Q-T interval was significantly prolonged at a serum potassium level less than 4.0 meq./liter. Nadler and associates[13] also found a statistically significant correlation between the Q-T interval and the serum potassium concentration in cases of diabetic acidosis with an identical R-R interval.

On the other hand, Currens and Crawford[5] and others were unable to demonstrate any consistent correlation between the electrocardiogram and the serum potassium level.

The significance of a changed intracellular potassium level for these electrocardiographic changes has been discussed by Nadler and associates,[13] Eliel and associates,[6] as well as by Currens and Crawford.[5]

It cannot be considered as definitely established whether these electrocardiographic changes are directly connected with the decreased plasma potassium level, if they are an expression of an intracellular potassium deficiency, or if they depend also on other factors.

It is well known that ACTH and cortisone, as well as desoxycorticosterone acetate induce changes in the potassium metabolism. Hypokalemic electrocardiograms after treatment with ACTH have been described by Bellet and associates,[3] Eliel and associates,[6] and Reeder and Goodrich.[15]

Our aim has been to study the electrocardiogram and the potassium metabolism in a number of cases of rheumatoid arthritis during administration of ACTH, cortisone, and desoxycorticosterone acetate.

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These studies were aided by grants from the Medical Research Council of Sweden.

The ACTH was kindly put at our disposal by Dr. C. H. Li, Berkeley, Calif.; the cortisone by Ciba Produkter AB., Stockholm, Sweden, and Merck and Company, Inc., Rahway, N. J., and the desoxycorticosterone acetate by Ciba Produkter AB., Stockholm, Sweden.

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MATERIAL AND METHODS

Case Reports

CASE 1.—S. A. H. B., a man, born in 1908, was a typical case of rheumatoid arthritis with symptoms since 1938. In general, there was a progressive deterioration with periods of more acute relapses. At examination before treatment with ACTH, the heart and circulatory system were considered normal. Blood pressure was 110/70 mm. Hg.

CASE 2.—P. E. E., a man, born in 1897, had had rheumatoid arthritis since 1948, rapidly progressing up to 1950. On examination in 1950 before treatment with ACTH, his general condition was fairly good. The circulatory system was normal. Blood pressure was 110/70 mm. Hg.

CASE 3.—E. A. L. was a man, born in 1904. There had been slowly progressive rheumatoid arthritis since 1937. When examined before cortisone administration, his general condition was fairly good. The circulatory system was normal. Blood pressure was 115/75 mm. Hg.

CASE 4.—V. C. O. was a man, born in 1923. He had suffered from rheumatoid arthritis since 1945. In 1950 the patient acquired an acute rheumatic pleuritis on the left side. Concomitant with this, pathologic electrocardiographic changes appeared. He improved rapidly, but the electrocardiographic changes remained; these were low, isoelectric, or negative T waves in Leads II, IV R, and CR_7. These changes were still observed at the beginning of hormone administration in December, 1950. On examination he was a complete invalid with ankylosis of most of the larger and smaller joints. Circulatory system was negative to physical examination. Blood pressure was 120/80 mm. Hg.

The Electrocardiogram

Electrocardiograms were recorded every third or fourth day during control periods and periods of hormone administration. Leads I, II, III, CR_2, IV R, and CR_7 were examined. The amplitudes were measured with an accuracy of 0.5 mm. from an isoelectric line constructed through the P-Q segments. The Q-T interval was measured in Lead II. The upper limit of normal for the Q-T interval at the heart rates present were calculated according to Ljung's formula:[9]

$$\text{Upper limit} = 0.2\ (\text{R-R interval}) + 0.22 \text{ second}$$

In each lead, amplitudes and intervals were measured in at least three complexes, and the mean was calculated.

The Q-T interval stated under Results represents the difference between the Q-T interval measured and the highest normal Q-T value as obtained according to Ljung's formula.

The electrocardiograms were considered unchanged when the alterations did not amount to:

for the P-Q interval:	0.03 second
for the QRS interval:	0.02 second
for the Q-T interval:	0.01 second
for the S-T segments:	a decrease in Leads I to III of 1 mm.; in precordial leads of 1.5 mm.
for the T waves:	a decrease in Leads I to III of 1.0 mm.; in the precordial leads of 2.0 mm.
for the U waves:	0.5 mm.

Balance Studies

The patients were studied in the metabolic unit of the hospital. They were given a constant diet and a constant supply of fluid during the control periods and the periods of hormone administration.

The nitrogen and potassium balances were calculated from the output of these substances in urine and feces. The potassium determinations were made with the Beckman flame photometer, Model DU. A detailed report on the methods used is given by Luft and Sjögren.[11]

Potassium derived from muscle protoplasm was calculated from: K (in meq.) = $2.7 \times N$, where N = nitrogen in grams.

Total body potassium was calculated from the amount of potassium exchangeable with the radioactive potassium isotope K^{42}. Equilibrium was supposed to be attained forty-eight hours after administration of K^{42}. The dose given was approximately 100 microcuries. Exchangeable potassium* was calculated from:

$$\text{K-exchangeable} = \frac{\text{K}^{42}\text{-injected} - \text{K}^{42}\text{-excreted}}{\dfrac{\text{K}^{42}\text{-urine}}{\text{K}^{39}\text{-urine}}}$$

RESULTS

Electrocardiogram Changes

Study 1.—Case 2. Control period of twelve days, ACTH protein 13 mg. per day for twelve days; control period of thirty-five days, ACTH protein 25 mg. per day for ten days.

The electrocardiograms during the control periods were normal. Mean values of the electrocardiograms of the first control period: pulse rate 80, P-Q interval 0.17 second, QRS interval 0.10 second, Q-T interval +0.02 second; S-T segments isoelectric in all leads; T_3 negative, other T waves positive; a U wave in Leads II and CR_2 of 0.5 and 1.0 millimeter.

Treatment.—The pulse rate fell from 80 per minute to 55 to 57. P-Q and QRS intervals were unchanged. Q-T intervals increased by 0.01 to 0.03 second. S-T segments were unchanged. T waves: in Leads I and II the amplitude increased by 0.5 to 1 mm., in the precordial leads the increase was 0.5 to 2.0 mm. U waves were lacking in Leads I and III; in Leads II and CR_2 the U wave increased by 0.5 mm., in IV R a U wave appeared with an amplitude of 0.5 millimeter.

Comments.—No pathologic electrocardiographic changes were recorded during treatment. The increase in the amplitude of the T waves and U waves and the appearance of U waves in Lead IV R could be ascribed to the lowering of the pulse rate.

Study 2.—Case 1. ACTH protein 13 mg. per day for fourteen days, control period of twenty-one days; 25 mg. per day for twelve days, control period of twelve days; and 50 mg. per day for 11 days, control period seventeen days.

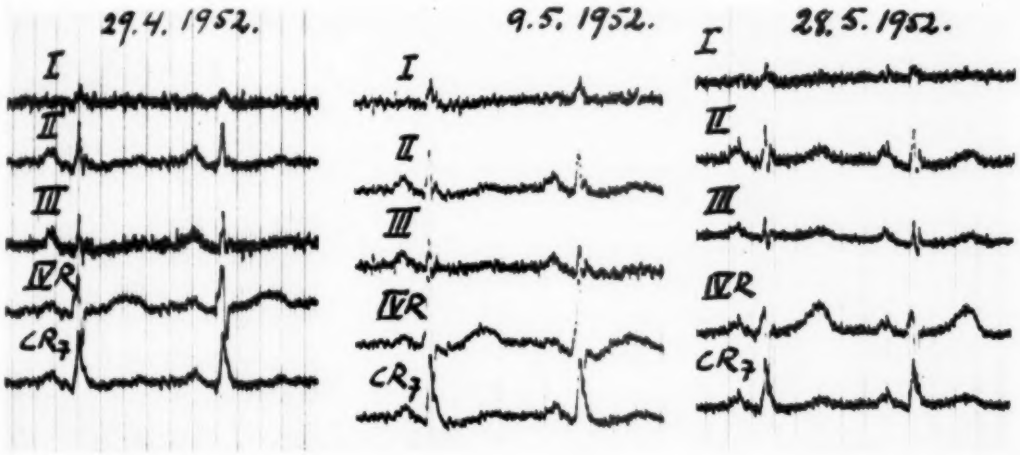
*K^{42} was supplied by the Atomic Energy Research Establishment, Didcot, Harwell, England.

The electrocardiograms were normal during all control periods. The following values concern the electrocardiograms at the end of the first control period: pulse rate 83, P-Q interval 0.19 second, QRS interval 0.10 second, Q-T interval ±0 second; S-T segments in Lead IV R ÷ 1 mm., in all other leads isoelectric; T waves positive; no U waves.

Treatment.—The pulse rate decreased during every ACTH period, the mean pulse rate during the control periods being 88 and during the ACTH periods 60 per minute. The P-Q, QRS, and Q-T intervals as well as the S-T segments remained unchanged. T waves: in Leads I to III, IV R and CR_7 were unchanged, in CR_2 a decrease by 2.0 to 2.5 mm. to a value of + 3.0 to + 4.0 mm. U waves with an amplitude of 1.0 mm. appeared in Lead II, of 0.5 to 1.5 mm. in Leads III, CR_2, IV R and CR_7.

Comments.—The decrease in the amplitude of the T waves in Lead CR_2, despite the fall of the pulse rate, may be looked upon as pathologic findings. The appearance of U waves during ACTH treatment may, however, be due to the decrease in the frequency.

Study 3.—Case 3. ACTH protein 80 mg. per day for twenty days, control period of eighteen days. Fig. 1.



A. *B.* *C.*

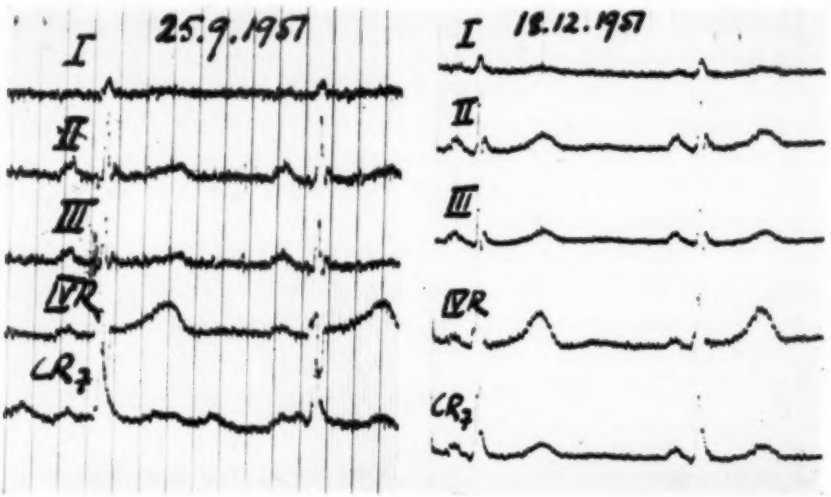
Fig. 1. (Study 3).—ACTH protein, 80 mg. per day for twenty days. *A*, Electrocardiogram on the 2nd day of treatment. *B*, Electrocardiogram on the 12th day of treatment. *C*, Electrocardiogram eleven days after discontinuation of treatment.

The electrocardiograms during the control period were normal: pulse rate 82, P-Q interval 0.15 second, QRS interval 0.10 second, Q-T interval ± 0 second, S-T segments isoelectric; T waves positive; no U waves.

Treatment.—The pulse rate remained unchanged. P-Q and QRS intervals unchanged. The Q-T intervals increased by 0.01 to 0.02 second. The S-T segments were unchanged in all leads. In T waves: the amplitudes decreased in Lead II by 2.0 mm., in Lead III by 1.5 mm., in CR_2 by 2.0 mm., and in Lead IV R by 4.0 mm., reaching the values of + 1.0, + 0.5, + 5.0 and + 2.0 mm., respectively; the T waves remained unchanged in Leads I and CR_7. U waves did not appear.

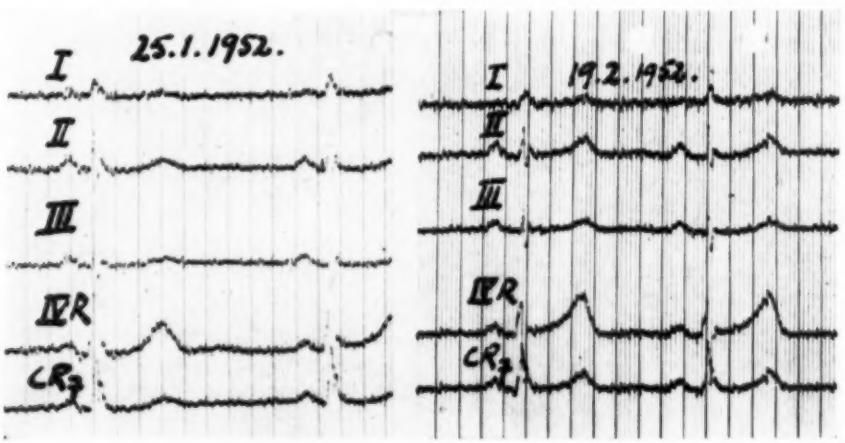
Comments.—The decrease in the T waves may be attributed to the administration of ACTH.

Study 4.—Case 3. Control period of twenty-five days, cortisone 200 mg. per day for seventy-six days, control period of twenty-seven days. Fig. 2.



A. *B.*

Fig. 2. (Study 4).—Cortisone 200 mg. per day for seventy-six days. *A*, Electrocardiogram forty-seven days before treatment. *B*, Electrocardiogram on the thirty-eighth day of treatment.



C. *D.*

Fig. 2. (Study 4).—*C*, Electrocardiogram on the sixty-sixth day of treatment. *D*, Electrocardiogram twenty-six days after discontinuation of treatment.

The electrocardiograms during the control periods were normal with the following mean values concerning the first control period: pulse rate 83, P-Q interval 0.14 second, QRS interval 0.10 second, Q-T interval ±0 second, S-T segments isoelectric; T waves positive; U wave of 0.5 mm. in Leads CR_2 and IV R.

Treatment.—The pulse rate fell from 83 to 55 to 60 per minute. P-Q and QRS intervals unchanged. The Q-T intervals increased by 0.03 second. The S-T segments were unchanged in all leads; in the posttreatment period an elevation of 0.5 mm. was noted in Leads II, III, CR_2 and IV R. T waves: the amplitudes increased in Leads II and III by 0.5 to 1.5 mm., in CR_2 by 1 to 4 mm., in IV R by 3 mm., in CR_7 by 0.5 to 2.0 millimeters. This increase remained during the posttreatment period. U waves: the amplitude increased by 0.5 mm. in Leads CR_2 and IV R, U waves appeared inconstantly in Leads II, III and CR_7, and was lacking in Lead I; the U waves in Leads CR_2 and IV R disappeared during the posttreatment period.

Comments.—Disregarding the minor increase in the U wave, which may be ascribed to the lowering of the pulse rate, no pathologic electrocardiographic changes were recorded during cortisone administration.

Study 5.—Case 3. Control period of sixteen days, cortisone 200 mg. per day for twenty-eight days, control period of forty days.

The electrocardiograms during the control periods were normal with the following mean values concerning the first control period: pulse rate 87, P-Q interval 0.15 second, QRS interval 0.08 second, Q-T interval ± 0 second; S-T segments + 0.5 mm. in Leads IV R and CR_7, in other leads isoelectric; T waves positive; no U waves.

Treatment.—The pulse rate was essentially unchanged (80 to 90 per minute). P-Q and QRS intervals were unchanged. The Q-T intervals increased by 0.01 to 0.02 second. S-T segments were unchanged. The T waves decreased in Leads II, III, IV R and CR_7 with 1.0 to 2.0, 1.0, 2.0 to 3.5 and 1 to 2 mm., respectively, reaching the values of + 1.0, + 1.0, + 3.5 and + 1.0 mm., respectively. A U wave of 0.5 mm. appeared in Lead IV R and CR_7.

Comments.—The decrease in the T waves and appearance of U waves may be attributed to the cortisone administration.

Study 6.—Case 4. Control period of twenty-five days, desoxycorticosterone acetate 20 mg. per day for sixty days.

The electrocardiograms during the control period were pathologic: pulse rate 82, P-Q interval 0.16 second, QRS interval 0.10 second, Q-T interval ÷ 0.01 second; S-T segments isoelectric; T waves negative in Leads II and CR_7 with an amplitude of ÷ 0.5 mm.; U waves of 1.0 and 0.5 mm. in Leads CR_2 and IV R, respectively.

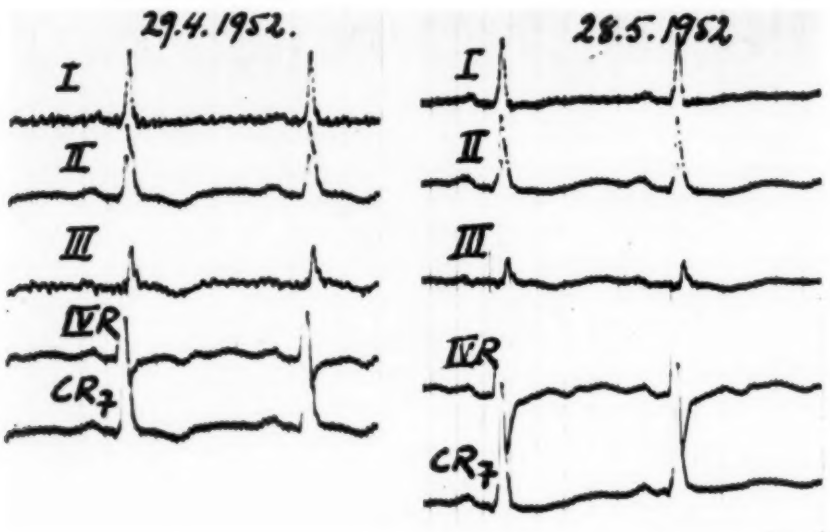
Treatment.—The pulse rate fell from 80 to 65 to 70 per minute. The P-Q and QRS intervals were unchanged. Q-T intervals increased by 0.03 to 0.06 second. The S-T segments were unchanged. T waves: an increase in Lead I by 0.5 mm., in IVR by 1 mm.; in Leads II and CR_7 the negative T waves became positive with an amplitude of 1 mm.; in Lead III the positive T waves became negative with an amplitude of ÷ 1.0 mm.; in Lead CR_2 they were unchanged. U waves: during treatment there was an increase in Leads CR_2 and IV R by 0.5 mm., an inconstantly appearing U wave of 0.5 mm. in CR_7.

Comments.—The electrocardiogram during the pretreatment period was pathologic with negative T waves in Leads II and CR_7. During treatment these pathologic changes became less pronounced, the T waves in these leads became positive. This development of the electrocardiogram may be considered a sign of a myocarditis in a phase of healing, and not necessarily as an effect of desoxycorticosterone acetate. However, the prolongation of the Q-T intervals may be considered as an effect of desoxycorticosterone acetate administration.

Study 7.—Case 4. Control period of thirty-four days, desoxycorticosterone acetate 30 mg. per day for thirty-four days, control period of twenty days.

The electrocardiograms during the control periods were pathologic with the following mean values concerning the first control period: pulse rate 83, P-Q interval 0.16 second, QRS interval 0.10 second, Q-T interval ÷ 0.02 second; S-T segments isoelectric; T waves ÷ 1 mm. in Lead II, negative in Lead III, otherwise positive; U wave of 1.0 mm. in Lead CR_2, of 0.5 mm. in IV R.

Treatment.—The pulse rate unchanged (80 to 85 per minute). P-Q, QRS and Q-T intervals as well as S-T segments were unchanged. T waves were unchanged. U waves increased by 0.5 mm. in Leads CR_2 and IV R.



A. *B.*

Fig. 3. (Study 8).—Desoxycorticosterone acetate 20 mg. per day for forty-three days. *A*, Electrocardiogram 7 days before treatment. *B*, Electrocardiogram on the twenty-first day of treatment.

Comments.—The only electrocardiographic changes obtained during desoxycorticosterone acetate administration was the small increase in the U waves.

Study 8.—Case 4. Control period of eight days, desoxycorticosterone acetate 20 mg. per day for forty-three days. Fig. 3.

The electrocardiograms during the control period were pathologic: pulse rate 82, P-Q intervals 0.16 second, QRS intervals 0.10 second, Q-T intervals ÷ 0.01 second; S-T segments isoelectric; T waves isoelectric in Lead I, negative in Leads II, III, IV R and CR_7, positive in CR_2. U wave 1.0 mm. in Leads CR_2 and IV R.

Treatment.—The pulse rate was unchanged. P-Q and QRS intervals were unchanged. The Q-T intervals increased by 0.01 second, S-T segments were unchanged. T waves: were unchanged in Leads I, II, III, IV R and CR_7, decreased by 2.0 mm. in Lead CR_2 they reached a value of + 3.0 mm. U waves were unchanged.

Comments.—The electrocardiograms remained unchanged, disregarding the minor change in the T waves in Lead CR_2.

TABLE I. POTASSIUM BALANCE, EXCHANGEABLE POTASSIUM AND POTASSIUM IN PLASMA DURING TREATMENT WITH ACTH, CORTISONE AND DESOXYCORTICOSTERONE ACETATE

SERIES OF ELECTRO-CARDIO-GRAMS NO.	CASE NO.	TREATMENT		POTASSIUM BALANCE		EXCHANGEABLE POTASSIUM		PLASMA POTASSIUM MEQ./LITER	
		DRUG	DAYS	TOTAL MEQ.	CORRECTED* MEQ.	DAYS OF PERIOD	TOTAL CHANGE MEQ.	BEFORE TREATMENT	FINAL VALUE
1	2	ACTH							
		13 mg./day	12					3,9	2,6
		25 mg./day	10					3,3	2,4
2	1	ACTH							
		13 mg./day	14	− 240	− 20			3,9	3,1-3,3
		25 mg./day	12	− 280	− 80			3,6	2,2-2,8
		50 mg./day	11	− 300	− 110			3,8	2,2-2,3
3	3	ACTH							
		80 mg. day	22	− 370	+ 90	22	− 350	3,9	2,6
4	3	Cortisone							
		200 mg./day	76	− 610	+ 210	18	− 100	4,4	3,1-3,3
						52	− 500		
5	3	Cortisone							
		200 mg. day	28	− 250	+ 30			4,3	3,8
*6	4	DCA							
		20 mg. day	60	− 60	+ 15	13	− 100	4,3-4,5	2,8
						46	− 100		
7	4	DCA							
		30 mg. day	34	− 220	− 185			4,2	3,1
8	4	DCA							
		20 mg. day	43			21	− 150	4,3	2,8-3,0
						43	− 150		

*These figures have been derived from the total balance after correction for the nitrogen loss.
DCA = desoxycorticosterone acetate.

POTASSIUM METABOLISM

The results are summarized in Table I. Administration of ACTH gave a significant decrease in the plasma potassium level. In Studies 2 and 3 the potassium and nitrogen balances were examined. The total balance showed a significant loss of potassium, which could mainly be ascribed to the protein break-

down. An extra potassium loss, that is potassium loss not accounted for by the protein breakdown, was obtained in Study 2. However, this loss was insignificant and amounted to less than five per cent of total body potassium. In Study 3 there was actually a retention of corrected potassium. Cortisone also gave a significant lowering of the plasma potassium level. In Study 4 there was a retention of intracellular potassium (that is "corrected potassium"). In Study 5 the potassium lost commensurated the loss of nitrogen. Desoxycorticosterone acetate depressed the plasma potassium significantly, and evoked an extra loss of potassium in one of the two studies, in which the potassium balance was examined.

DISCUSSION

Only minor electrocardiographic changes occurred in our cases after administration of ACTH, cortisone and desoxycorticosterone acetate. In one of the ACTH cases (Study 2) there appeared a small decrease in the amplitude of the T wave in Lead CR_2, and a U wave with a small amplitude in Leads II and III as well as in the precordial leads; in a second case treated with ACTH (Study 3) there was a moderate decrease in the amplitude of the T waves in Leads II, III, CR_2 and IV R. In one case treated with cortisone (Study 5) we observed a moderate decrease in the amplitude of the T waves in Leads II, III, IV R and CR_7, and at the same time a U wave with a small amplitude in IV R and CR_7 appeared. In one of the desoxycorticosterone acetate cases (Study 6) the Q-T interval increased by 0.03 to 0.06 second. In the remaining four studies—one each with ACTH and cortisone and two with desoxycorticosterone acetate—the electrocardiogram was considered unchanged during hormone administration. Though there was in two of these series an increase in the Q-T interval of 0.02 to 0.03 second, this change cannot be considered as significant (Osnes,[14] Ljung,[10]). If we exclude that experiment, where the Q-T interval increased by 0.06 second (Study 6), those electrocardiograms that showed changes during hormone administration still remained normal. In Study 4 the electrocardiograms were abnormal before treatment, but the pathologic findings did not increase during hormone administration. In some electrocardiograms the shape of the S-T intervals and T waves changed during hormone treatment (Fig. 3). In no case, however, was a typical and pronounced hypokalemic electrocardiogram observed.

In all studies the plasma potassium decreased significantly during the administration of ACTH, cortisone as well as desoxycorticosterone acetate and reached—except for Study 5—values of 2.2 to 3.3 meq. per liter. During the administration of ACTH and cortisone a considerable loss of potassium was found. It is reasonable to believe that most of this potassium loss is due to a decrease of body protein, as the potassium loss was accompanied by a negative nitrogen balance. In Table I the column "corrected potassium balance" denotes the potassium that is not accounted for by the nitrogen balance. It can thus be seen that ACTH in larger doses may or may not give rise to a small extra potassium loss. Cortisone did not give rise to any potassium loss, not explicable by the nitrogen loss. There was actually a retention of intracellular potassium in Study 4.

Desoxycorticosterone acetate caused a loss of potassium amounting to 60 and 220 meq., respectively. After correction for the changes in the nitrogen

balance there was no extra potassium loss in the former study, while there was a loss of 185 meq. in the latter one. The changes in the potassium balance at desoxycorticosterone acetate administration were mainly found during the first week of treatment.

Summarizing our findings we thus obtained a significant decrease in plasma potassium to levels usually considered as hypokalemic. There was, on the other hand, no evidence of larger losses of intracellular potassium. The electrocardiograms showed only minor alterations, and typical hypokalemic changes did not appear.

Our findings show that there was no correlation between a depression of the plasma potassium level and the electrocardiogram. This has also been found in other conditions by Currens and Crawford[5] and Eliel and associates.[6] We were unable to observe the correlation between the Q-T interval and plasma potassium that was described by Bellet and associates.[3] The material of these authors consisted of patients, in whom the simultaneous occurrence of an intracellular potassium deficiency was most probable.

The concentration of intracellular potassium was not determined in our studies. A decrease in the volume of intracellular fluid might counteract a simultaneous loss of intracellular potassium with respect to the concentration of this ion. On the other hand, an increase in the intracellular fluid volume might cause a decrease in the concentration of potassium in face of potassium retention. We were able to demonstrate indirectly in Studies 3 and 4 an increase in the volume of intracellular fluid of a magnitude sufficient to decrease the intracellular potassium concentration (Luft and Sjögren, to be published). The relative potassium deficit was not larger than 10 per cent of total body potassium. It has also been claimed in earlier metabolic work with ACTH and cortisone (Bartter and associates,[1] Luft and Sjögren[11]) that intracellular fluid was retained during treatment.

SUMMARY

The electrocardiogram and the potassium metabolism were studied in cases of rheumatoid arthritis during administration of ACTH, cortisone and desoxycorticosterone acetate. ACTH protein (Li) was given in daily doses of 13 to 80 mg. for ten to twenty-two days, 200 mg. of cortisone per day was given for twenty-eight and seventy-six days, and desoxycorticosterone acetate in daily doses of 20 and 30 mg. for forty-three, sixty and thirty-four days.

A significant decrease in the plasma potassium level to hypokalemic values was obtained. The change of intracellular potassium, not accounted for by changes in protoplasm, was not larger than 10 per cent of total body potassium.

No typical hypokalemic electrocardiograms were observed. There was no correlation between changes in the electrocardiograms and the plasma potassium level.

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THE EFFECT OF THE VALSALVA MANEUVER ON THE CIRCULATION. II.

The Role of the Autonomic Nervous System in the Production of the Overshoot

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IT HAS been shown in a recent report from this department that the expected circulatory responses of a Valsalva maneuver are absent in cases with significant mitral stenosis.[1] The absence of the normal responses has also been found to occur in other types of heart disease[2,3] as well as after sympathectomy[4] and ganglionic blocking agents.[5,9] Further insight into the mode of action of the autonomic nervous system on the Valsalva maneuver was sought by observing the changes in venous pressure simultaneously with those of arterial pressure and heart rate in normal individuals, and by noting the alterations in response after atropinization and tetraethylammonium chloride.

MATERIALS AND METHODS

All patients had a normal cardiovascular system at the time of study. However, Case 3 exhibited a low resting arterial blood pressure, and Case 5 had a transient blood pressure elevation at the time of the test, presumably due to excitement.

Pressures were obtained by puncture of the brachial artery and the antecubital vein and were recorded on a direct writing polyoscillograph,* using capacitance-type electromanometers,* simultaneously with an electrocardiographic Lead II. On command the patient blew directly into the mercury manometer for as long as he was able, and the height of the mercury column was noted. The patient's cheeks were supported by the hands of one of the observers during the maneuver. The relationship of the intraoral to the intrapleural pressure has been presented elsewhere.[6]

No attempt was made to standardize the height of the intraoral pressure or the length of time of straining. It has been our experience, in these and other

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cases, that a satisfactory pressure overshoot and bradycardia will result following a Valsalva maneuver if the period of straining is long enough and the intrapleural pressure during straining high enough to produce a marked elevation of peripheral venous pressure and a definite lowering of the pulse pressure in Phase 2. This was effected in all cases presented here before and after drug administration.

In one group of tests, tetraethylammonium chloride was injected intravenously until symptoms (such as visual disturbances, sense of warmth, and lightheadedness) appeared or a maximum of 400 mg. had been given. In another group of tests on other patients, 2 mg. of atropine was given intravenously. In each experiment two Valsalva maneuvers were performed before and after injection of either drug.

DISCUSSION OF RESULTS

For convenience the Valsalva maneuver is divided into four phases in this report as has been customary in the past. Phase 1 is at the onset of straining, phase 2 is the steady state of straining, Phase 3 is the period immediately following the cessation of straining, and Phase 4 is the next period during which the events return to normal.

The results are assembled in Tables I to III and illustrated in Figs. 1 to 5.*

The present study shows that tetraethylammonium chloride abolishes the overshoot in arterial pressure and the bradycardia following straining, while atropine increases the magnitude and duration of the overshoot, but abolishes the bradycardia. Venous pressure response is not altered by either drug.

Our results suggest that initially on straining (Phase 1), the sudden increase in intrathoracic pressure is transmitted directly from the aorta to the systemic peripheral arteries. In addition, blood is "squeezed" from the lungs into the systemic circuit. These effects cause a sudden rise in arterial pressure and the secondary reflex slowing of the heart. This reflex bradycardia is abolished by atropine and tetraethylammonium chloride, the former acting as a vagal blocking agent, the latter as a generalized ganglionic blocking agent.[7,8]

During sustained increased intrathoracic pressure (Phase 2) systolic pressure normally remains at or slightly below the control values, the diastolic pressure rises and the rate increases markedly.† After atropine administration, the diastolic pressure also rises, although there is a fall in systolic pressure. The rate increases to the same extent as before drug administration. After tetraethylammonium chloride, both the systolic and diastolic pressures fall and the rate increase is small. This would seem to indicate that there is stimulation of the sympathetic nervous system during Phase 2 before drug administration and after atropine administration, which is blocked by tetraethylammium chloride. This confirms Bunnell's observation on tetraethylammonium chloride.[9] The

*In Case 5, in which the blood pressure was elevated because of excitement at the time of testing, and in which the control response to the Valsalva maneuver differed slightly from the other cases, tetraethylammonium chloride lowered the pressure to the average range of the group, and the response to the Valsalva maneuver after its use was the same as in the others of this group.

†The slight elevation of systolic and pulse pressures near the end of prolonged straining in a few instances is attributed to the fact that venous pressure may approach intrapleural pressure at this time, leading to a small increase in ventricular filling.

stimulus to the sympathetic system appears to be the hypercapnea and hypoxia developed during the Valsalva maneuver acting through chemoreceptors. When there is a fall in arterial blood pressure, this too may stimulate the sympathetics via pressor receptors.

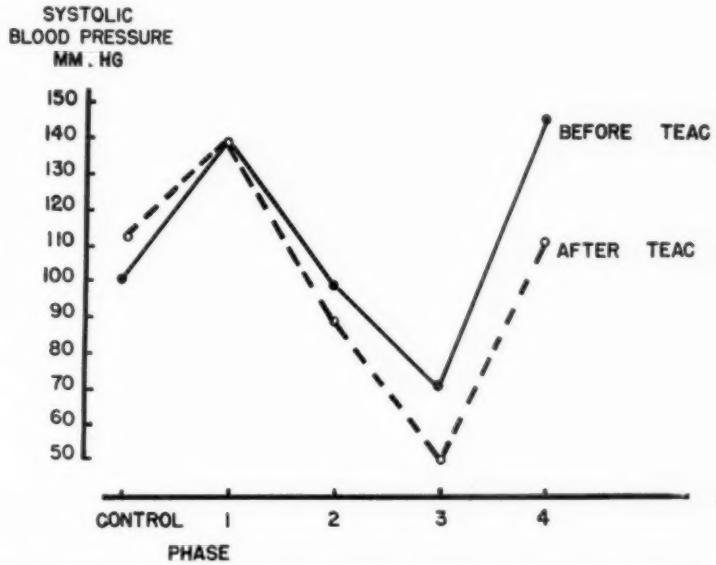

Fig. 1.—Systolic pressure (mm. Hg) plotted against phases of the Valsalva maneuver before and after the administration of tetraethylammonium chloride. Note the lack of overshoot after drug administration. (Discussed in text.)

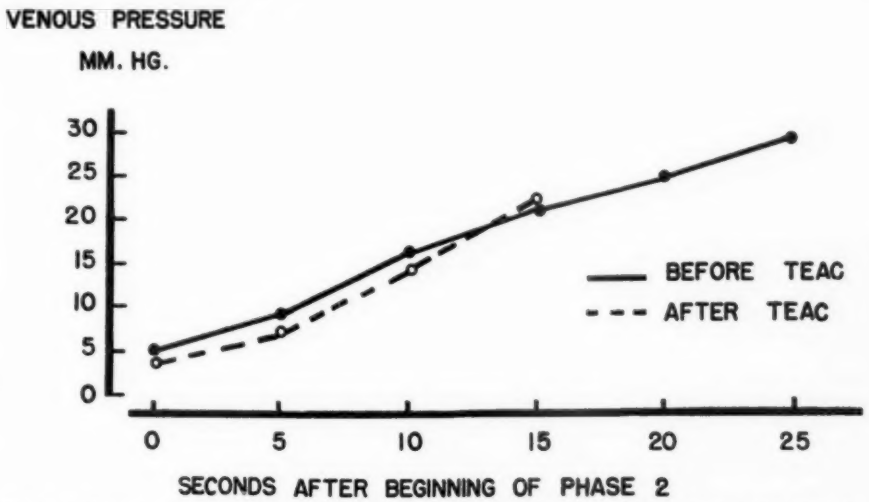

Fig. 2.—Venous pressure (mm. Hg) plotted against seconds of straining during the Valsalva maneuver before and after the administration of tetraethylammonium chloride. (Discussed in text.)

Immediately after the cessation of straining (Phase 3) there is further sympathetic stimulation, in the normal and atropine groups, by the fall in blood pressure which is the mechanical result of release of increased intrathoracic pressure.

TABLE I. SYSTEMIC BLOOD PRESSURE AND PULSE RATE RESPONSE TO THE VALSALVA MANEUVER BEFORE AND AFTER DRUG ADMINISTRATION*

CASE		DOSE (mg.)	CONTROL			PHASE 1			PHASE 2			PHASE 3			PHASE 4			L.O.P.
			S	D	R	S	D	R	S	D	R	S	D	R	S	D	R	
Tetraethylammonium Chloride																		
1.	BD	120	107	63	75	135	100	60	110	90	111	70	50	115	142	80	60	48
	AD		114	72	77	150	106	72	96	78	100	43	36	107	114	64	107	54
2.	BD	400	104	64	60	126	78	48	100	75	86	70	54	88	132	82	50	35–40
	AD		119	78	65	140	90	64	88	62	71	42	30	75	119	80	75	44
3.	BD	400	74	33	63	117	71	64	73-99	55-75	93	58	38	100	112	51	59	60
	AD		93	58	81	112	78	81	68	55	91	37	28	94	91	60	100	40
4.	BD	400	120	67	86	172	140	86	70–118	62–104	107-125	78	60	143	192	98	67	60
	AD		122	78	94	144	112	94	100	80	94	78	60	100	118	78	107	100
Average	BD		101	57	71	138	97	65	98	79	102	69	51	112	145	78	59	52
	AD		112	72	79	137	97	78	88	69	89	50	39	94	111	71	97	60
5.†	BD	250	210	116	103	274	188	111	210	188	167	174	142	167	318	190	86	70
	AD		142	82	100	180	118	100	70	56	130	22	16	136	140	79	130	70

Atropine

6.	BD	2	148	82	90	192	106	63	150-162	120-126	100-77	110	78	103	190	100	50	60
	AD		117	82	125	130	100	125	84–132	78-122	137-150	110	96	150	200	140	136	60
7.	BD	2	110	58	81	160	110	79	78	62	103	30	23	111	160	78	65	60
	AD		119	73	107	168	124	107	78	70	125	38	36	125	190	102	128	60
8.	BD	2	129	86	83	144	96	86	106	88	120	92	76	125	154	96	68	50
	AD		104	70	103	122	78	103	83-98	66-80	136-142	66	58	150	164	116	137	50
9.	BD	2	100	59	81	132	78	71	104	80	115	74	50	115	140	80	59	40
	AD		106	70	115	140	102	115	70	60	125	50	40	150	198	130	140	48
Average	BD		122	71	84	157	98	77	111	88	107	77	57	114	161	89	61	53
	AD		112	74	113	140	101	113	87	76	133	66	58	142	188	122	135	55

Key

BD = Before drug administration.
AD = After drug administration.
S = Systolic blood pressure (mm. Hg).
D = Diastolic blood pressure (mm. Hg).
R = Heart rate in beats per minute.
I.O.P. = Intraoral pressure (mm.Hg) during straining.

*In the control period, Phase 1, and in Phase 3 this is the average; in Phases 2 and 4 this is the greatest deviation. When, however, two values are given in Phase 2, the first is the average value of the temporary steady state and the second is the greatest deviation near the end of the phase.

†Not included in average because elevated blood pressure before drug administration is considered to be due to excitement.

TABLE II. VENOUS PRESSURE (mm. Hg) IN THE CONTROL PERIOD AND AT FIVE SECOND INTERVALS DURING SUSTAINED STRAINING (PHASE 2)

CASE		SECONDS					
		0	5	10	15	20	25
Tetraethylammonium Chloride							
1.	BD	3–4	10	18	24	28	35
	AD	—	—	—	—	—	—
2.	BD	7–8	11	15	20	22	25
	AD	5–7	12	20	28	—	—
3.	BD	2–3	7	14	18	23	26
	AD	1–2	5	11	16	—	—
4.	BD	—	—	—	—	—	—
	AD	3	5	11	—	—	—
Average	BD	4.5	9	16	21	24	29
	AD	3.5	7	14	22	—	—
5.*	BD	3	13	22	32	40	—
	AD	2	9	17	22	—	—
Atropine							
6.	BD	10	19	28	40	46	48
	AD	11–12	19	24	34	38	—
7.	BD	2–3	22	33	—	—	—
	AD	1–2	14	25	30	—	—
8.	BD	9–10	12	17	22	—	—
	AD	5	8	12	15	20	25
9.	BD	5	8	11	15	18	—
	AD	3	5	9	13	—	—
Average	BD	7	15	22	25	32	—
	AD	5	12	18	23	29	—

BD = Before drug administration.
AD = After drug administration.
*Not included in average because systemic pressure was elevated due to excitement before drug administration.

A few seconds after the end of the Valsalva maneuver (Phase 4), blood which was dammed back in the venous system under increasing pressure during straining forcefully enters the constricted peripheral arterial system. A marked overshoot in arterial pressure results and is followed a few beats later by a reflexogenic bradycardia and a slight vasodilatation. This interpretation is in accord with that reached by Sarnoff and associates[10] in animal studies.

After tetraethylammonium chloride, the lack of bradycardia in Phase 4 is due to the absence of an overshoot in arterial pressure, the stimulus for the

TABLE III. SUMMARY OF OBSERVED EFFECTS OF TETRAETHYLAMMONIUM CHLORIDE AND ATROPINE

	NORMAL	AFTER TEAC*	AFTER ATROPINE
Resting blood pressure		Generally rises in this series	Inconstant
Resting pulse rate		Slight increase	Marked increase
Phase 1	Sudden increase in blood pressure. Heart rate generally slows	Sudden increase in blood pressure. Heart rate unchanged	Sudden increase in blood pressure. Heart rate unchanged
Phase 2	Pulse pressure low, systolic pressure at or slightly below control values, diastolic pressure elevated above control. Marked heart rate increase	Pulse pressure low, systolic pressure definitely below control values, diastolic pressure below control. Slight heart rate increase	Pulse pressure low, systolic pressure below control values, diastolic pressure elevated above control. Marked heart rate increase
Phase 3	Low systolic and pulse pressures. Heart rate increases	Low systolic and pulse pressures. Heart rate slightly increased	Low systolic and pulse pressures. Heart rate increase
Phase 4	Pressure overshoot. Bradycardia	No pressure overshoot. Slight heart rate increase	Exaggerated overshoot. Heart rate considerably above control
Venous pressure	Gradual rise during straining	Similar to normal but 1 mm. Hg lower	Similar to normal but 1 mm. Hg lower

*TEAC = Tetraethylammonium chloride.

reflexogenic effect. The lack of the pressure overshoot after straining in subjects receiving tetraethylammonium chloride appears to be the result of the blocking of sympathetic vasopressor reflexes which normally cause systemic vasoconstriction. Apparently the amount of blood dammed back in the venous system during straining is of the same order before and after tetraethylammonium chloride because it has been shown that there is no change in the venous pressure response after administration of this drug. Under these circumstances it would appear that the ability of the blood pumped into the systemic arteries to run off into the capillaries determines whether or not an overshoot will occur. Therefore, tetraethylammonium chloride, by preventing the reflexogenic vasoconstriction that is normally present in Phase 4, leaves the peripheral systemic arterioles wide open to permit the blood stored in the veins during straining to run out of the arteries about as fast as the heart pumps it in; thereby, the overshoot is avoided.

After atropine administration, there is an increased overshoot in Phase 4 without a bradycardia, the latter the result of the blocking of the parasympathetic nervous system. The exaggerated overshoot may be due to the effect of the increased heart rate permitting more rapid evacuation of the blood retained

in the veins during straining, but it may also be due to the sympathetic nervous system acting unopposed at this time, thereby reducing the rate of runoff into the capillaries.*

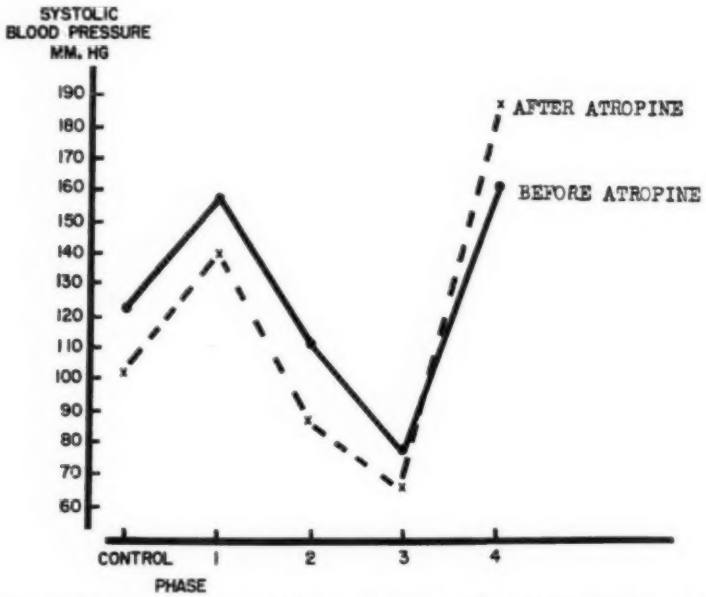

Fig. 3.—Systolic blood pressure (mm. Hg) plotted against phase of the Valsalva maneuver before and after the administration of 2 mg. of atropine. Note increased overshoot in Phase 4 after atropine. (Discussed in text.)

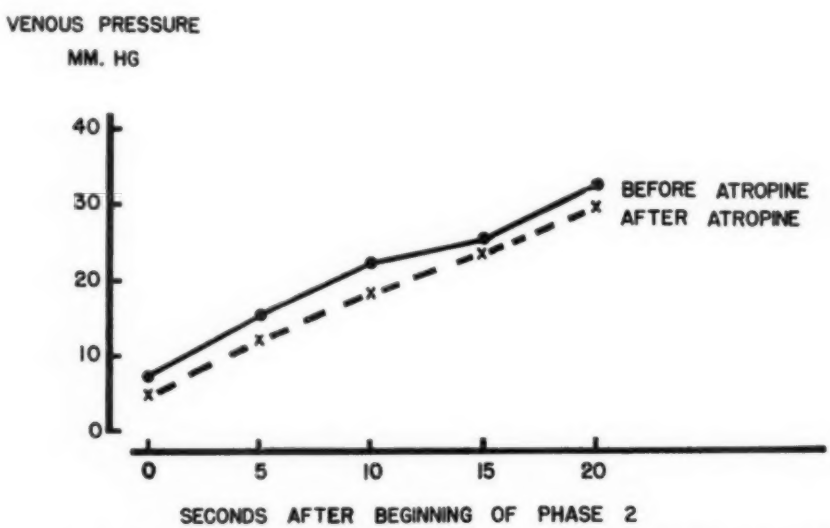

Fig. 4.—Venous pressure (mm. Hg) plotted against seconds of straining during the Valsalva maneuver before and after the administration of atropine. (Discussed in text.)

*It is suggested that a test for complete atropinization may be one in which, after the administration of atropine, reflex bradycardia is prevented and an overshoot in pressure develops in Phase 4 of the Valsalva maneuver.

All normal patients we have studied have shown essentially the same results. However, Kay and associates[11] recently have reported that at least two of ten normal patients studied by their method failed to have an overshoot in Phase 4, although still showing a bradycardia in this phase. From our study, and from examination of the records of approximately fifteen other patients in whom a

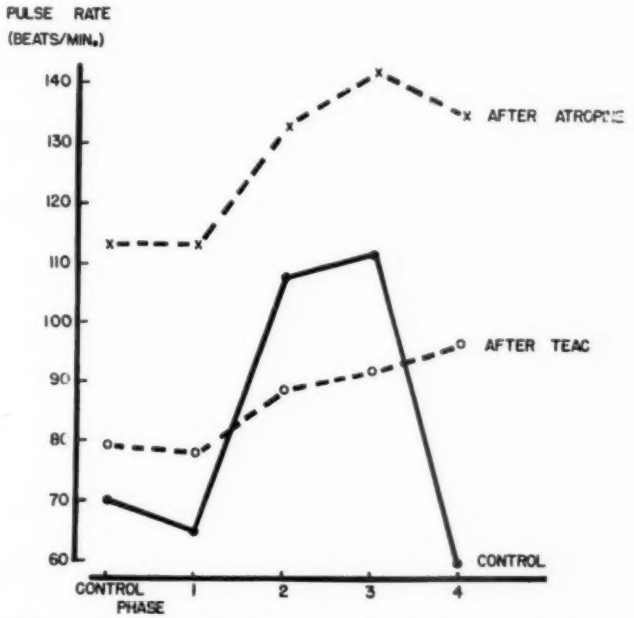

Fig. 5.—Heart rate (beats per minute) plotted against phases of the Valsalva maneuver before and after the administration of tetraethylammonium chloride and atropine. (Discussed in text.)

bradycardia was present in Phase 4, it would appear that the bradycardia is always dependent upon the pressure overshoot, since we have never found it to occur in the absence of the latter. This conclusion is confirmed by Matthes.[12] However, the degree of the bradycardia is not necessarily a function of the degree of overshoot.

Our studies to date indicate that the overshoot and bradycardia following straining may be blocked by several mechanisms. If the vasopressor reflexes are blocked by sympathectomy or drugs and the systemic arterioles are dilated or in their normal state of tone in the post-straining period, the increased cardiac output following the Valsalva maneuver will not produce an effect. On the other hand, for example, if the reflexes are intact, yet insufficient blood reaches the periphery because of a narrowed mitral orifice, the overshoot and bradycardia following straining also are not seen. This is apparently true as well in constrictive pericarditis, heart failure, and pulmonary vascular disease, as we have recently found in studies now in progress.[3*]

*It is beyond the scope of this paper to discuss the electrocardiographic changes during and following the straining. However, in one case, definite S-T depression with an associated T-wave inversion occurred, beginning in Phase 2 and reaching a peak several seconds after the cessation of straining. This change began before the overshoot, and it was just as evident in Phases 2 to 4 after tetraethylammonium chloride administration when the overshoot had been abolished.

SUMMARY

1. Mitral valvular disease prevents the overshoot in blood pressure and bradycardia normally seen after a Valsalva maneuver. It does so by preventing sufficient blood from reaching the periphery in the post-straining period despite normal reflexes.

2. Tetraethylammonium chloride also prevents this overshoot and bradycardia by blocking vasopressor reflexes during and immediately after sustained straining.

3. Atropine blocks the parasympathetic nervous system, and the overshoot in pressure in Phase 4 is exaggerated and prolonged, while the bradycardia is abolished. Increased cardiac output after atropine acting in the presence of a constricted arterial system may partially explain the exaggerated overshoot in Phase 4.

4. Venous pressure rises in a similar manner during straining, even after the administration of tetraethylammonium chloride or atropine.

We are indebted to the volunteers who were the subjects of this study, and to Dr. Gerald Graham for drawing our attention to the studies of Matthes.

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EXPERIMENTALLY-INDUCED PETECHIAL HEMORRHAGE AND WHITE EMBOLIZATION IN THE RABBIT'S NICTITATING MEMBRANE

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METHODS for testing cutaneous capillary fragility have been based on the appearance of petechial hemorrhages induced by applying varying degrees of positive or negative pressure to the skin. This investigation deals with a new method of approach[1], measuring, microscopically, cutaneous capillary fragility based on the effect of hemorrhagic agents applied to minute or capillary vessels. The degree of resistance of these vessels to the formation of petechiae is used as an index of capillary strength.

The vessels of the nictitating membrane of the rabbit's eye were chosen for the observations. The technique involved ascertaining the minimum effective concentration of a given hemorrhagic agent locally injected. In addition, the effect of systemic injection of an agent was observed on the vessels of the nictitating membrane. The nictitating membrane, a well-circumscribed area, has proved to be most satisfactory both as to good visibility of the capillary blood vessels and as to the constancy of their reactions to applied hemorrhagic agents. Other sites, the conjunctiva, the shaved skin of the abdomen, and of the ear, were found less satisfactory.

A number of test agents produced white emboli in the nictitating membrane. Earlier observations by Copley[2,3] on the production of white emboli by heparin were corroborated by several investigators.[4-7] Since such minute emboli may contribute to the production of petechial hemorrhage, possible correlations between the occurrence of both phenomena are presented.

It will be shown that sodium salts of heparin and of Merthiolate, generally considered innocuous, may produce petechial hemorrhages even in therapeutic dosages, and, in the case of heparin, also white emboli.

PROCEDURES

1. *Techniques.*—The rabbit is fastened on a simply designed, sloping board which can be easily moved about on the table. The elevated end of the board

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is forked and the rabbit, lying on the board in the opisthotonos position, is so placed that its head hangs downward in the fork. The head is thus immobilized and the stretched hindlegs are tied down at the distal part of the board. The forelegs are inserted under two hooks, one on each side of the board near the fork. Under these conditions the animal does not struggle and remains quiet for the three-hour period of the experiment.

A. *Intradermal tests.*—Preliminary experiments were done with the aid of a 5-power magnifying lens on the nictitating membrane, conjunctiva of the eyelids, and the shaved outer ear and skin of the abdomen. The amount of the test substance injected into the nictitating membrane and the conjunctiva was about 0.05 and 0.1 c.c.; that which was injected into the denser cutaneous tissues of the inner and outer side of the external ear and into the abdominal skin varied from 0.1 to 0.4 c.c. All the injections were intradermal, employing a 27-gauge needle and tuberculin syringe.

B. *The nictitating membrane technique.*—Observations were made on the outer or convex surface of the nictitating membrane, which is an anchor- or shield-shaped structure situated at the medial angle of the eye. Pressure exerted on the eyeball causes the nictitating membrane to slide forward over the medial anterior surface of the bulb. Kingsley[8] described a fold of typical conjunctival epithelium which is reflected over the outer two-thirds of the nictitating membrane except at the tip, where the epithelium is stratified, squamous, and often heavily pigmented. The epithelium rests upon a layer of white fibrous connective tissue in which the capillaries are situated. A hyaline, anchor-shaped cartilage is in the center of the nictitating membrane.

A 27-gauge hypodermic needle was inserted intradermally, close to the medial angle of the eyelids and, in order to minimize leakage to the outside, the tip was carried toward the middle of the membrane where the injection was performed. The inserted needle tip was kept as close as possible to the surface, and care was taken not to rupture the resulting wheal, the amounts of the test substance injected being about 0.05 and 0.1 c.c. The observations were made with a 4-power ocular and a 12.5-power objective of a binocular dissecting microscope from which the stage was removed.

The extent of the hemorrhagic effects was noted by the number of localized extravasated spots, petechiae, which appeared after a given treatment. From the time of appearance of the first petechia, the number and distribution of further developing petechiae were noted at intervals of five to fifteen minutes over a period of three hours.

II. *Lines of Approach.*—The investigations concerning the microhemorrhagic effects of the test substances on the nictitating membrane followed three lines of which only the first was studied extensively. About 300 healthy male rabbits were used; each weighed approximately 1.5 to 3.5 kilograms.

A. *Local introduction of agents.*—These were: (1) Merthiolate (sodium ethyl mercuri thiosalicylate), (2) Shiga protein toxin (ST 37 neurotoxin), (3) moccasin snake venom, (4) croton oil in mineral oil, (5) sodium heparin, (6) heparin plasma, (7) saline plasma, (8) citrate plasma, (9) serum, (10) *Clostridium welchii* toxin (300 mouse MLD/c.c.), (11) *Clostridium septicum* toxin #790A (300 mouse LD_{50}/c.c.), (12) streptolysin *streptococcus pyogenes*, group A #791 (67 LD_{50}/c.c.), (13) cysteine hydrochloride, (14) tricresol. The following were the control agents: (15) mineral oil, (16) physiologic saline, and (17) distilled water.

B. *Systemic introduction of agents.*—These were (1) 1 per cent sodium heparin, (2) 1 per cent sodium heparin combined with 1:2,000 Merthiolate, (3) 1:2,000 Merthiolate, (4) citrate plasma with 1:10,000 Merthiolate.

C. *A combination of local and systemic introduction.*—This was done with a systemic injection of heparin and the local injection of Merthiolate 1:10,000 and of 0.5 and 5.0 per cent croton oil.

OBSERVATIONS

I. *Petechiae and White Emboli.*—A petechia appears as a red-colored, round- or oval-shaped lesion, and is localized in the tissue resulting from extravasated blood. The size has been arbitrarily chosen to measure up to approximately 1.5 mm. in longest diameter. With some substances one was able to observe in the center of the petechia a light, yellowish-colored spot giving the petechia a targetlike appearance.

The persistence of the petechia is related to its original size. Small petechiae may be seen to disappear in the customary time of observation of three hours. Large petechiae, however, have been observed to persist for three days or longer. As the petechiae disappear, they are changed to red fogs which spread in all directions. The intensity of these red fogs decreases with time until no degree of redness can be detected. Dilatation of the blood vessels, congestion, and a decrease in the speed of the blood flow always accompany the appearance of petechiae. Red fogs, other than those due to disappearing petechiae, can often be seen along the course of a vessel. Such red fogs might well be due to extravasated red blood cells. It is also possible that these fogs represent the products of hemolysis.

Follow-up observations on subsequent days were made on the nictitating membrane. As a result there appeared to be a complete restoration of the blood vessels from three to five days following the use of Merthiolate, Shiga protein toxin, and moccasin venom. On the other hand, the vascular damage caused by the injection of croton oil did not appear to be repaired even after several weeks.

With croton oil, a great number of white emboli appeared in the blood stream of the nictitating membrane. These emboli enlarged in size as they moved along. They were observed to block the vessels, the blood being forced to travel by another route. Later, when this route also became blocked, the vessels ruptured and caused extensive hemorrhages, appearing as large petechiae and ecchymotic areas. The blood vessels may have been damaged by erosion as well as by increased pressure due to blockage. When croton oil was injected into the nictitating membrane, sloughing resulted after two days, and the tissue never recovered. In fact, when intradermal injections of croton oil were used in the rabbit's ear, extensive edema developed and was followed by areas of dry gangrene. These areas finally sloughed completely or formed large holes in the rabbit's ear. The higher the concentration of croton oil used, the larger were the resulting necrotic areas. Croton oil produced extensive embolization with resulting hemorrhage followed by necrosis. When heparin was first injected into the ear vein, the croton oil was found to have an increased effect, and the size of the white embolizing bodies was markedly enlarged.

Shiga protein toxin produced small petechiae which at times tended to become confluent. Because of this, difficulties in making counts were encountered. Occasionally white emboli were observed. However, capillary hemorrhages never were observed to be due to blockage. The petechiae were seen to fade rapidly in some instances which also made counting difficult. The petechiae appeared mainly near small vessels.

Small petechiae of similar size were produced with moccasin venom. They were confluent, well-discernible, and could be counted with ease and better than those produced by any of the other agents. As a rule, white emboli were seen only rarely, and those observed were of small size. The petechiae were observed anywhere in the capillary bed.

With Merthiolate the petechiae were small. They tended to become confluent at a late stage of the test period in contrast to those produced by moccasin snake venom. The petechiae appeared in the minute and larger vessels and tended to fade rather rapidly. White emboli were only rarely observed.

Serum produced petechiae in the minute capillaries. Small white emboli were always observed. It appears from experiments with serum to which Merthiolate is added that petechiae occur possibly because of direct damage of the endothelial layer and/or the cells. These petechiae were seen either in the middle of a larger vessel, or nearby; the petechiae still permitted circulation. On the other hand, with serum alone the petechiae were smaller and more terminally located on minute capillaries as if they resulted from the white emboli blocking and rupturing them.

With sodium heparin or heparin plasma, white emboli were observed to block the minute capillaries, and occasionally rupture of these vessels occurred at the site of blockage. These

emboli were of large size. Saline plasma also produced white emboli blocking the minute vessels where petechiae occurred. The emboli were numerous, as with heparin plasma, but with both plasmas they were smaller in size than the emboli produced with croton oil. Citrate plasma produced white emboli. Petechiae formed in the minute blood vessels. The tendency to block or obstruct the minute or terminal capillaries was found to be less pronounced with citrate plasma when compared to saline or heparin plasma.

No difficulties were encountered in making petechial counts except when large numbers of petechiae occurred suddenly. In such instances there tended to be fusion or merging of petechiae. Many such areas could be found towards the end of the experiment and the redness, obviously mainly due to extravasation, was of varying shades possibly because of the merging of petechiae. It should be pointed out that the intensity of the redness may have been augmented by increased amount of blood due to vasodilatation. Pressure on the nictitating membrane was avoided in order to obtain blanching which better differentiates the two kinds of redness. This was to eliminate any additional contributing factors, such as positive pressure, which of itself produces petechiae.

The numbers of petechiae observed at given successive times were plotted on graphs. The average number of petechiae at time intervals of 30, 60, 90, 120, and 180 minutes was taken from these graphs. The data given on the tables indicate the rate of occurrence of petechiae during the three-hour test period.

II. *Petechial Counts Following Local Injection.*—

A. *Merthiolate*: It had been planned to use a dilution of 1:10,000 Merthiolate solution as a preservative in order to eliminate bacterial infection of the test solutions. In running such a control experiment with Merthiolate in 0.9 per cent sodium chloride solution, we were surprised to find the appearance of a large number of petechial hemorrhages in the nictitating membrane within a short period of time following injection. This led to the investigation of this effect by the use of preparations from three different lots of Merthiolate, kindly supplied by Dr. E. J. Teeter of Eli Lilly & Company.

In a series of sixteen rabbits, Merthiolate from these lots was employed in four different concentrations in 0.9 per cent sodium chloride solution: 0.01, 0.005, 0.002, and 0.001 per cent. Since 0.05 c.c. of these concentrations was injected in each instance, the corresponding actual quantities amounted to 5.0, 2.5, 1.0, and 0.5 gamma. In Table I the results of the average petechial counts are summarized. Usually the first occurrence, not shown on Table I, amounted to only one petechia. In three instances two petechiae occurred at once and in one instance three petechiae. In one other case, not included in Table I, as many as forty petechiae occurred simultaneously. An explanation for the latter uniquely high number cannot be given. The possibility exists that this particular nictitating membrane had some abnormality, although it was not apparent.

TABLE I. THE LOCAL PRODUCTION OF PETECHIAE BY MERTHIOLATE AND MOCCASIN SNAKE VENOM

TEST SUBSTANCE IN PHYSIOLOGIC SALINE	CONCENTRATION	NUMBER OF TESTS	AVERAGE PETECHIAL COUNTS AFTER:				
			30 MIN.	60 MIN.	90 MIN.	120 MIN.	180 MIN.
Merthiolate	0.5	6	0	1	2	3	2
	1.0	6	1	3	5	6	10
	2.5	5	4	12	16	19	26
	5.0	14	10	26	35	38	39
Moccasin snake venom	0.5	3	4	12	24	33	36
	0.8	6	5	12	17	21	18
	2.5	3	29	43	52	58	60

Our data show that the first occurrence of petechiae is related to the concentration of Merthiolate. The higher concentrations produce petechiae after a shorter interval of time. Furthermore, the number of petechiae was also found to be related to the concentration of Merthiolate. However, this relationship is not as clear-cut as that concerning the onset of petechiae. As a rule the two higher concentrations were injected into the nictitating membrane of one rabbit and the two lower ones into a second rabbit. In later experiments a control method was used: one rabbit was injected with A per cent and B per cent, and the other rabbit was injected with B per cent and C per cent. While this reduced the number of concentrations used, it helped to indicate the relative capillary strength of the two animals. For example, it was noted that, although the same concentration of Merthiolate was used, Rabbit R-34 developed six petechiae in ninety minutes, following the injection of 5 gamma into the left nictitating membrane. Rabbit R-50, on the other hand, developed eighty-nine petechiae in the same period of time. When 2.5 gamma were injected into the right nictitating membrane of both these rabbits, it was found that R-50 developed 23 petechiae in 120 minutes, while R-34 only eleven petechiae in the same period of time.

It was found that the injection of 1 gamma of Merthiolate into the left nictitating membrane of Rabbits R-36 and R-51 brought about close results up until ninety minutes had elapsed. After this time R-36 developed twenty-five petechiae in ninety minutes, while R-51 developed only two, and even those two disappeared in thirty minutes. Other rabbits showed almost identical numbers of petechiae after certain test periods and given quantities of Merthiolate. Rabbits R-36 and R-50, therefore, were considered susceptible to capillary weakening agents, while Rabbits R-34 and R-51 were considered resistant. Similar results were obtained with all three lots of Merthiolate.

In two Rabbits, R-52 and R-75, the same concentrations of Merthiolate were injected. A close similarity in the rate of development and the number of petechiae in the left nictitating membrane of both animals was noticed. In 180 minutes R-52 had twenty petechiae, while R-75 had thirty, following the injection of 5 gamma. When 2.5 gamma was injected into the right nictitating membrane of these animals, R-75 developed eight petechiae in 120 minutes while R-52 developed fifty-nine. It is possible that such a sudden sharp rise in petechiae is an artefact due to improper injection technique. The shallowness of the injection may be considered responsible, since it has been our experience that the more shallow the test substance is injected, the earlier the petechiae appear. Conversely, the deeper the injection of the test substance is carried, the longer it takes for the petechiae to appear. Sometimes no petechiae are observed at all after a very deep injection. We believe that diffusion of the test substance is an important factor.

It should be noted that these petechiae produced by Merthiolate disappear quickly so that actually the rate of increase is counted. Some petechiae disappear, but so many more are formed that at the time of the count there are more petechiae than there were previously.

B. *Moccasin snake venom.*—Table I summarizes also the microhemorrhagic effect of moccasin snake venom. Again, only the average petechial counts are listed. The first occurrence of multiple petechiae, not listed in the Table I, is produced with the high concentration of the venom. The two lower concentrations show close values both in the first occurrence and the average petechial counts. The average petechial count, obtained with the high concentration, is considerably increased as compared with those produced by the low concentrations. The venom, kindly supplied by Dr. S. M. Peck, was found to be a most powerful hemorrhagic agent.

C. *Shiga protein toxin.*—Results with this toxin, prepared and kindly supplied by Dr. R. J. Dubos of the Rockefeller Institute, are given in Table II. The concentrations used in twelve rabbits were 5.0, 1.0, 0.1 and 0.01 per cent. All the results with few exceptions indicated that the higher concentrations caused earlier ruptures than the lower ones. The number of petechiae and the extent of damage appeared to be directly proportional to the concentration of toxin injected. In some cases, however, it was not possible to carry out the experiment in making petechial counts throughout the three-hour period. The petechiae became uncountable due to increased numbers and to merging. It was noted that some rabbits have higher petechial counts than others, though the same concentration of test substance is used. This is due, as found with Merthiolate or moccasin venom, to individual variability in the capillary strength. Certain rabbits fall into a group which is susceptible to agents producing capillary lesions while others are more resistant.

In order to test possible variability in the capillary strength in the same rabbit, several experiments were carried out in which the same concentration of test substance was injected into both nictitating membranes of the rabbit. In two rabbits, a close similarity in counts between left and right nictitating membranes was found up to 120 minutes. It was only toward the end of the three-hour test period when the petechiae were no longer accurately countable that a slight difference appeared.

D. *Croton oil.*—Findings of petechiae with croton oil are also presented in Table II. Again we find a correlation between the concentration of the hemorrhagic agent, the average petechial counts, and also the average first occurrence.

TABLE II. PETECHIAL HEMORRHAGES PRODUCED LOCALLY BY SHIGA PROTEIN TOXIN, AND CROTON OIL IN VARIOUS CONCENTRATIONS

TEST SUBSTANCE (0.05 C.C.)	CONCENTRATION PER CENT	NUMBER OF TESTS	AVERAGE PETECHIAL COUNTS AFTER:				
			30 MIN.	60 MIN.	90 MIN.	120 MIN.	180 MIN.
Shiga protein toxin in physiologic saline	0.01	4	0	0	5	15	17
	0.1	4	0	4	14	35	C*
	0.5	7	0	10	28	64	C
	1.0	4	1	17	81	C	C
	5.0	4	3	37	98	C	C
Croton oil in mineral oil	0.5	4	0	4	17	24	C
	1.0	6	0	21	38	43	C
	5.0	10	2	14	25	31	C
	10.0	4	9	25	36	46	C

*C = countless

E. *Plasma and serum.*—A series of experiments were performed with serum and plasma which were obtained from rabbit blood by cardial puncture. The concentrations of plasma and serum were 5 per cent throughout. For better comparison the final plasma or serum concentration in physiologic saline or isotonic solution was maintained at 5 per cent. The hematocrit value was taken into account, when necessary, for the preparation of the different plasma solutions. Nine volume parts of 3.8 per cent sodium citrate were mixed with 1 volume part of blood, and the resulting citrate-plasma was diluted with physiologic saline to obtain the 5 per cent plasma concentration. The content of heparin amounted to 0.085 mg. per c.c. of the heparin-saline plasma. Thus the injected volume of 0.05 c.c. contained 4.25 gamma (or about one-half unit) of heparin. More petechiae were produced, as can be seen from Table III, with heparin plasma, saline plasma, and serum, whereas citrate plasma decreased significantly petechia formation. No significant differences were observed with homologous and autologous serum or the three anticoagulant-plasma systems.

F. *Sodium heparin.*—The local injection of heparin produced not only petechiae but numerous white emboli. There findings are presented in Table IV. Both nictitating membranes of two animals were injected with the same quantity of sodium heparin. The observation of the first occurrence of white emboli either was found to precede or occur simultaneously with the first occurrence of petechiae. The earlier occurrence of petechiae with the smaller concentration of 0.1 mg. of heparin seemed to indicate that Rabbit, R-164, was more susceptible than R-165 which was injected with 1 mg. and exhibited less petechiae within ninety minutes than R-164. The increase in petechiae in R-165 is marked only at the three-hour observation, thus apparently corresponding to the larger dosage of heparin.

G. *Other hemorrhagic agents.*—*Clostridium welchii* toxin and *clostridium septicum* toxin in 100 per cent concentrations, kindly supplied, respectively, by Dr. M. H. Adams and Dr. A. W. Bernheimer of New York University, produced numerous petechiae, whereas none resulted following injection with a 100 per cent concentration of streptolysin from *streptococcus pyogenes* Group A, prepared by Dr. Bernheimer. The microhemorrhagic action of 0.5 per cent or a total of 0.25 mg. cysteine hydrochloride on the nictitating membrane was investigated. Numerous white emboli were formed and many petechiae which increased in size were observed near the minute capillaries.

TABLE III. THE LOCAL PRODUCTION OF PETECHIAE WITH SERUM AND DIFFERENT TYPES OF PLASMA

TEST SUBSTANCE IN PHYSIOLOGIC SALINE	NUMBER OF TESTS	SCOPE	PETECHIAL COUNT AFTER:				
			30 MIN.	60 MIN.	90 MIN.	120 MIN.	180 MIN.
Citrate plasma	6	Range	0	0-2	0-3	0-7	0-18
		Average	0	0	1	3	8
Saline plasma	6	Range	0-3	1-11	4-50	14-67	0-75
		Average	1	5	19	24	24
Heparin plasma	4	Range	0-6	10-14	10-35	14-45	10-64
		Average	2	13	23	26	28
Serum	8	Range	0-7	0-47	0-65	0-51	0-50
		Average	4	12	24	23	23

The injection of 3 per cent tricresol or a total of 1.5 mg. resulted in first occurrence of petechiae after three minutes and the production of many petechiae during the three-hour test period. No white emboli were observed.

H. *Controls.*—Mineral oil was used as control for the croton oil experiments. Physiologic saline and sterile distilled water served as control for the other test substances. None of these agents produced petechiae.

TABLE IV. THE PRODUCTION OF WHITE EMBOLI AND PETECHIAE IN THE NICTITATING MEMBRANE BY THE LOCAL INJECTION OF HEPARIN

SODIUM HEPARIN (MG.)	RABBIT NUMBER	EYE	WHITE EMBOLI-FIRST OCCURRENCE AFTER MINUTES	PETECHIAL HEMORRHAGES						
				FIRST OCCURRENCE		COUNT AFTER:				
				MINUTES	COUNT	30 MIN.	60 MIN.	90 MIN.	120 MIN.	180 MIN.
0.1	R-164	Left	14	14	1	13	25	30	41	26
		Right	5	10	1	5	14	39	28	22
1.0	R-165	Left	18	24	1	2	5	9	30	116
		Right	22	22	1	2	6	14	32	140

III. *The Effect of Systemic Treatments.*—Table V shows the occurrence of white emboli and petechiae following the infusion of citrate plasma or serum with 1:10,000 Merthiolate in nine animals. The nictitating membranes of two out of six rabbits infused with citrate plasma and of one out of three animals infused with serum exhibited petechial hemorrhages. The maximum occurrence was one to three with citrate plasma and nine petechiae with serum. During the three-hour test period, six out of nine animals exhibited white emboli. With the exception of R-171 the

TABLE V. THE OCCURRENCE OF WHITE EMBOLI AND PETECHIAE IN THE NICTITATING MEMBRANE FOLLOWING THE INFUSION OF CITRATE PLASMA OR SERUM WITH MERTHIOLATE 1:10,000

RABBIT		INFUSION*		EYE	WHITE EMBOLI-FIRST OCCURRENCE AFTER MINUTES	PETECHIAL HEMORRHAGES			
						FIRST OCCURRENCE		MAXIMUM OCCURRENCE	
NUMBER	WEIGHT (KG.)	MERTHIOLATE 1:10,000 IN:	VOL. (C.C.)			COUNT	AFTER MINUTES	COUNT	AFTER MINUTES
R-211	1.8	Citrate plasma	18	Left	None	0	180	0	180
				Right	None	0	180	0	180
R-174	1.7	Citrate plasma	17	Left	None	0	180	0	180
				Right	None	0	180	0	180
R-171	1.5	Citrate plasma	15	Left	20	0	180	0	180
				Right	61	0	180	0	180
R-210	1.8	Citrate plasma	18	Left	36	0	180	0	180
				Right	40	0	180	0	180
R-209	1.5	Citrate plasma	15	Left	115	0	180	0	180
				Right	140	1	140	2	145
R-172	1.7	Citrate plasma	17	Left	10	1	14	3	100
				Right	11	1	11	1	11–155
R-212	1.5	Serum	15	Left	None	0	180	0	180
				Right	None	0	180	0	180
R-214	1.5	Serum	15	Left	55	0	180	0	180
				Right	60	0	180	0	180
R-213	1.5	Serum	15	Left	25	1	25	9	120
				Right	17	1	20	9	120

*An amount of blood is withdrawn and replaced by same volume of plasma or serum.

TABLE VI. THE PRODUCTION OF PETECHIAE AND WHITE EMBOLI IN THE NICTITATING MEMBRANE INDUCED BY SYSTEMICALLY INJECTED HEPARIN AND MERTHIOLATE

RABBIT	SODIUM HEPARIN (MG./KG.)	MERTHIOLATE (MG./KG.)	EYE	WHITE EMBOLI. FIRST OCCURRENCE AFTER MINUTES	PETECHIAL HEMORRHAGES			
					FIRST OCCURRENCE		MAXIMUM OCCURRENCE	
					COUNT	AFTER MINUTES	COUNT	AFTER MINUTES
R-203	20	0	Left	57	0	180	0	180
			Right	58	0	180	0	180
R-200	20	0	Left	35	0	180	0	180
			Right	20	1	20	2	40
R-201	20	0	Left	18	2	18	8	55
			Right	39	1	46	6	70
R-207	0	1	Left	None	0	180	0	180
			Right	None	0	180	0	180
R-208	0	1	Left	None	0	180	0	180
			Right	None	0	180	0	180
R-206	0	1	Left	0*	1	30	7	150
			Right	0*	1	50	3	90
R-204	20	1	Left	15	1	40	7	105
			Right	21	1	45	11	102
R-205	20	1	Left	10	1	10	20	85
			Right	11	1	11	20	34

*Emboli observed before injection.

first occurrence of white emboli was seen on both nictitating membranes after similar periods of time. In seven out of twelve nictitating membranes, emboli occurred without petechial hemorrhage. In all animals the volume of blood withdrawn from the heart amounted to 1 per cent of the body weight. This volume was replaced by an equal amount of plasma or serum.

In Table VI the findings with systemically injected heparin and Merthiolate are given. In the three rabbits, receiving only 20 mg. heparin per kilogram weight, white emboli were first observed between eighteen and fifty-eight minutes. Two of these animals exhibited petechiae, R-200 having petechiae only on the right nictitating membrane. In these cases, the first occurrences of white emboli were either simultaneously observed with the first occurrence of petechiae or preceded the latter by several minutes as on the right nictitating membrane of R-201. The injection of 1 mg. Merthiolate per kilogram weight did not result in any production of white emboli or petechiae in two animals, R-207 and R-208. The third rabbit, R-206, exhibited white emboli even before systemic injection. It is of interest that this rabbit was not previously used and did not appear to be ill. This rabbit exhibited petechial hemorrhages in both the nictitating membranes and the iris of the eyes. The combined injection of sodium heparin (20 mg. per kilogram) and Merthiolate (1 mg. per kilogram) resulted always in the production of petechiae and white emboli. In R-204 the white emboli were first seen after fifteen and twenty-one minutes while petechiae occurred after forty and forty-five minutes. In R-205, white emboli and petechiae were simultaneously observed after ten and eleven minutes. This experiment indicates that the capillary damage brought about was always manifest and was greater when heparin and Merthiolate were injected together.

Table VII demonstrates the effect of systemically injected heparin on the microhemorrhagic action of the local injection of Merthiolate in two animals and of croton oil in three animals. In all five animals heparin increased the effect of the hemorrhagic agent. However, this effect was more marked with croton oil than with Merthiolate with regard to the first occurrence of petechiae and the rate of increase in petechial counts. Five gamma Merthiolate and 5 per cent croton oil were injected into the nictitating membrane both before and immediately after systemic injection with 10 to 25 mg. heparin per kilogram weight. The local injections before heparinization served as control.

TABLE VII. THE EFFECT OF SYSTEMICALLY INJECTED HEPARIN ON THE MICRO-HEMORRHAGIC ACTION OF THE LOCAL INJECTION OF MERTHIOLATE AND CROTON OIL

RABBIT	INJECTION		FINDINGS	EYE	FIRST OCCURRENCE		PETECHIAL COUNT AFTER MINUTES:				
	SYSTEMIC SODIUM HEPARIN (MG./KG.)	LOCAL TEST SUBSTANCE			AFTER MINUTES	PETECHIAL COUNT	30	60	90	120	180
R-161	20	Merthiolate 5 gamma	Control	Left	14	1	8	10	8	17	20
			Experimental	Right	11	1	13	40	50	65	81
R-163	20	Merthiolate 5 gamma	Control	Left	19	1	10	25	27	34	44
			Experimental	Right	13	1	13	40	55	77	111
R-209	10	5 per cent croton oil	Control	Left	42	1	0	5	13	25	42
			Experimental	Right	20	1	7	24	39	48	C*
R-210	10	5 per cent croton oil	Control	Left	61	1	0	0	10	13	38
			Experimental	Right	25	1	4	33	57	C	C
R-122	25	5 per cent croton oil	Control	Right	31	1	0	3	5	4	C
			Experimental	Left	3	4	14	31	49	50	C

*C = countless

IV. *Macroscopic Observations.*—The appearance of the site of injection, the surrounding tissues, and the general condition of the animal were noted at various time intervals. Outline, shape of vessels and signs of diapedesis were recorded. Pin point to pinhead sized red to purple spots were designated as petechiae, whereas larger areas with dark purple spots which appeared confluent were designated as ecchymoses.

Abdominal intradermal injection was found not to be suitable for macroscopic observations, apparently because of the thickness of the skin.

Croton oil was used in concentrations of 5 to 100 per cent in mineral oil. The 100 per cent concentration when applied in 0.2 c.c. amount resulted in death of the animal. Autopsy revealed petechiae in the lungs but not in the intestines or the mesentery. Following injection of croton oil into the outer ear, excessive edema developed. Around the site of injection were multiple petechiae and ecchymotic areas. Either the entire outer ear or its larger part was swollen to such an extent that it could no longer be kept erect but dropped with increasing size of the ear. The edema was found to have an anteroposterior diameter on some areas measuring up to 2 cm. thickness. Following the edema, a large area of necrosis developed with resulting dry gangrene and finally with sloughing of the entire outer ear or the part involved. The development of the necrotic area appeared to be different from the one produced by the *clostridium welchii* toxin, the latter being less extensive and without the excessive edematous reaction. In using a small (0.2 c.c. of 5 per cent) concentration of croton oil, the ear developed rather circumscript punched-out areas, the edges of which healed well.

Moccasin snake venom, when injected into the ear lobe and the nictitating membrane in concentrations of 1:1,000 to 1:3,000, produced petechiae which either occurred immediately or within several hours with the exception that the 1:3,000 preparation did not produce petechiae in the outer ear.

On injecting a 10 per cent concentration of Shiga protein toxin into either the nictitating membrane or into the skin of the ear, petechiae occurred almost immediately. In all instances in which 0.1 or 0.2 c.c. of the 100 per cent concentration was injected, death ensued after four days. When the latter concentration was injected into the nictitating membrane, exophthalmus of the corresponding eye resulted, indicating that there occurred increased capillary permeability.

Streptolysin *streptococcus pyogenes* Group A did not exhibit petechiae except in one instance where a few appeared following 0.3 c.c. intradermal injection into the ear. Erythema was the only noticeable reaction at the site of injection. It is of interest that two rabbits which were injected intradermally into the ear and the nictitating membrane with 0.25 to 0.35 c.c. streptolysin and 0.25 to 0.3 c.c. of 0.5 per cent cysteine hydrochloride died and the autopsy revealed pulmonary hemorrhages. Another animal which was injected in the ear lobe with 0.2 c.c. streptolysin and 0.2 c.c. of the cysteine hydrochloride solution survived.

Clostridium septicum and *clostridium welchii* toxins produced petechiae almost immediately following injection. Erythema was marked around the area of petechial hemorrhages and ecchymoses. A peculiar blanching phenomenon was observed at the site of injection with the *welchii* toxin. The blanched area contained numerous petechiae. After several days the area became necrotic.

Mineral oil and physiologic saline which were used as controls throughout these experiments never resulted in petechial hemorrhage.

The injection of 5 mg. of sodium heparin into the nictitating membrane or the outer ear resulted in petechiae, and occasionally small hematomas were seen. Animals which were injected locally in the outer ear or the nictitating membrane with 0.2 c.c. of 5 per cent croton oil or of 1:2,000 moccasin snake venom and systemically with 20 to 40 mg. of heparin per kilogram weight exhibited increased numbers of capillary hemorrhages at the sites of local injection.

DISCUSSION

This investigation deals mainly with the production of petechiae, as induced by applying test chemicals directly to blood capillaries under observation. Since the various test agents which were employed presumably have different effects

upon the different components of the blood vessel wall, and also upon different blood constituents, there may be various mechanisms in the breakdown of the integrity of the vessel wall leading to petechial hemorrhage. Copley[9] has advanced the concept that the phenomena of capillary fragility and of capillary hemorrhagic diathesis are not identical, as is generally believed. The degree of capillary fragility can be estimated by the petechial count, whereas capillary hemorrhagic diathesis is dependent upon both capillary fragility and hemostasis, and can be detected by the occurrence and the degree of ecchymosis. Several factors are concerned in capillary fragility or the degree of "breaking strain" of minute blood vessels.[9] Petechiae caused by chemical and those caused by physical means were differentiated. The accumulation of minute thrombi or emboli may contribute to the resultant decrease in the degree of breaking strain of the capillary wall. In many instances the presence of emboli was found in the capillary bed of the nictitating membrane without simultaneous occurrence of petechial hemorrhages. Thus the mechanical cause of damage to a capillary blood vessel by the formation of a thrombo-embolus does not seem to be sufficient. Some combination of intravascular, vascular, and perivascular factors seems to be needed to produce a petechial hemorrhage.

The observations were limited to male animals. There may be hormonal effects on capillary fragility associated with the estrous cycle. This phase of the problem needs investigation, especially since some authors claimed increased capillary fragility in female human subjects during or before menstruation.

Of interest for clinical consideration are the findings on the petechia-producing effect of agents which are in general therapeutic use as ingredients in preparations for parenteral injection into patients. Such substances were Merthiolate in concentration of 1:10,000 and tricresol in 0.3 per cent concentration. It appears from these observations that, in subjects with initially increased capillary fragility or capillary hemorrhagic diathesis, the use of these substances may be potentially dangerous.

It was found that plasma obtained with various anticoagulants (or by dilution with physiologic saline) and serum may weaken the capillary wall. Comparative studies on various rabbit plasma anticoagulant systems and with serum obtained from the same blood withdrawal, all adjusted to the same concentration of plasma or serum, showed that citrate plasma had less of an effect upon capillary fragility than had serum or other plasma systems. More studies are needed to evaluate these findings.

The observed subsequent disappearance of a petechia or the recovery of the lesion may be explained by the closure or plugging of the capillary wall by agglutinated blood platelets, and the absorption of the extravasate via the lymph channels. It is not known to us whether any of the test agents has any inhibiting action on platelet agglutination.

Our observations on variations in susceptibility in different individual rabbits likewise appear to be significant. We were able to differentiate between the resistant and the susceptible animal. The former exhibited more capillary strength than the latter when tested by certain agents. Copley and Kozam[10] also found this in human subjects upon using the negative pressure principle for

making petechial counts. They observed petechial production following the application of negative pressure of 600 mm. Hg on the internal brachial region. In some individuals no or very few petechiae were produced, while in others numerous petechiae resulted. From these observations, employing two different methods for the production of petechiae in man and in rabbit, it may be concluded that capillary fragility varies in different healthy subjects.

Comparative findings on the nictitating membranes of both eyes in one rabbit suggest the existence of variations in capillary strength of analogous tissues in the same animal. Upon repeated testing of human subjects wide variations have occasionally been encountered in the petechial counts in the same general area at about the same time.[10] Thus the petechial count, as measured by well-controlled methods using the negative pressure principle or, as in this presentation, by the injection of test agents, cannot be expected to be an accurate measure for capillary fragility. Repeated tests in different animals using the same agent under the same experimental conditions are recommended to prevent misinterpretation of results.

No attempt was made to relate variations of the petechial count with areas of different capillary richness. The vascularity may differ, for example, by the opening of previously closed capillaries. There may also be differences in the total extent of the capillaries. Such differences would be significant in comparing the nictitating membrane of rabbits weighing 1.2 kilograms with those weighing 3.5 kilograms. Increased vascularity may prove to be a significant factor in evaluating the susceptibility of animals to the microhemorrhagic action of this or that test agent.

The administration of heparin, although considered more advantageous than any other substance in the treatment of thrombo-embolic phenomena, may constitute, in certain individuals, a hazard, because of the possible formation of capillary hemorrhages. The effects of heparin on the inhibition of several stages of the blood coagulation process, and on the production of platelet agglutination, may be augmented by the additional effect of heparin in increasing capillary fragility as well. The mode of action of heparin in reducing the strength of the capillary wall needs to be clarified.

Our findings demonstrate that a combined local and systemic administration of heparin decidedly increases capillary fragility. Since heparin or a similar substance is considered as the physiologic anticoagulant for maintaining the fluidity of blood, there may be other substances, normally present in blood, which counteract its weakening action on the capillary wall. Perhaps heparinization of the animal may not only induce platelet agglutination[11,12,13] and thus white emboli, but may also have a direct weakening effect on the capillary wall.

An objection might be raised concerning the validity of using locally injected agents for testing capillary fragility. The disturbance of local homeostasis thus produced at the site of injection, concomitant with the formation of a wheal, might make it difficult to evaluate the petechiae-producing effect of the same agents introduced systemically. Although this problem cannot be entirely settled without further experiments, the following findings appear significant. Streptolysin from *streptococcus pyogenes*, Group A, when injected locally, did not

produce petechiae. Thus, not even such a complex, chemically impure substance is necessarily capable of producing petechiae by local homeostatic disturbances alone.

It should be pointed out that the prior systemic introduction of heparin seems to condition the capillary bed of the nictitating membrane, so that upon the use of a local test agent more petechiae were produced. This increase was greater than can be explained by a mere addition of effects resulting from one, systemic heparinization and two, from the locally applied test agent. This is illustrated in Tables VI and VII.

It is obvious that appreciably higher concentrations could be utilized when applied locally than when administered systemically. This may explain why the systemic application of an agent is not as effective in producing petechiae as local application. Increasing minute concentrations of locally injected test agents yielded relatively larger numbers of petechiae. A partial explanation of the hemorrhagic action of heparin may be in the production of platelet-agglutination thrombi,[2-7] which block the capillary vessel and therefore rupture the capillary from within. From another view, the lack of platelets from the resulting thrombocytopenia may leave open larger interendothelial pores in accordance with Danielli's notion.[11] The platelet-agglutinating action of heparin thus could be visualized as affecting the capillary wall in two ways. The over all effect of heparin in the production of petechial hemorrhage includes the above platelet-agglutination effect as well as a possible softening effect upon the endothelial wall.

Croton oil was chosen as a test substance, because it was known to produce hemorrhages in the intestinal mucosa. When this agent was used in the nictitating membrane, the large emboli which were formed obstructed the capillary bed with resulting hemorrhages into the tissues, edema, and subsequent necrosis or gangrene. The production of croton oil shock in rabbits by Hoeber[15] might be in part explained by the mechanical obstruction of the capillary circulation by emboli. Croton oil was the only substance used in our investigations which was found to produce emboli, hemorrhage, and edema.

Another problem concerns the effect of serum in the production of capillary hemorrhage. The mode of action is obscure, although serum is known to produce platelet agglutination.[11] Moreover, serum contains proteolytic enzymes which may contribute to hemorrhage production. It remains to be shown which of these enzymes, present in the circulation, have a hemorrhage-inducing action and upon which structural part of the blood vessel.

SUMMARY

1. Various hemorrhagic agents were injected intradermally into ear, abdomen, conjunctiva, and nictitating membrane of about three hundred non-anesthetized male rabbits, and biomicroscopic observations were made at the site of injection.

2. Different areas of the skin of the same animal differed in the degree of petechial production with the same test agent. Because of this finding these

regions were not considered conducive to any approach of a quantitative nature. The best region found for observational studies of petechial hemorrhage was the nictitating membrane.

3. A new technique which utilizes both nictitating membranes of the rabbit's eyes was developed and is described to test the fragility of the minute blood vessels within a three-hour test period by the time of occurrence and number of petechiae.

4. At a given dosage administered, a correlation was found between the number and the time of occurrence of petechiae. When different dosages were used, the number produced correlated directly with the dosage. Physiologic saline, distilled water, and mineral oil served as controls and did not produce petechiae.

5. It was possible to divide the animals into two groups, those susceptible and those resistant to induced hemorrhage by a given test agent.

6. Individual variations were found in the reparability of the damaged vessels. Some animals repaired these vessels in a few hours, while others required days.

7. The following agents were used locally to produce petechial hemorrhage in the nictitating membrane: Merthiolate, Shiga protein toxin, moccasin snake venom, croton oil in mineral oil, sodium heparin, heparin plasma, saline plasma, citrate plasma, serum, *clostridium welchii* toxin, *clostridium septicum* toxin, streptolysin *streptococcus pyogenes* Group A, cysteine hydrochloride, and tricresol.

8. Capillary ruptures induced by croton oil are probably due to the formation of large particles which embolize. The embolization of these vessels leads to their rupture and petechial manifestation.

9. The local or systemic injection of heparin results in the constant occurrence of white emboli in the nictitating membrane. It appeared that these emboli were of a different nature than those produced by croton oil.

10. The local injection of heparin always resulted in petechiae in the nictitating membrane, although the systemic injection of heparin alone did not necessarily result in petechiae. Systemic heparinization combined with Merthiolate always produced petechiae in the nictitating membrane.

11. When local application of Merthiolate or croton oil was preceded by the systemic injection of sodium heparin, more petechial hemorrhages resulted.

12. The first occurrence of white emboli preceded or was observed simultaneously with the first occurrence of petechiae. Such emboli were not, or only rarely, observed following injections of moccasin snake venom and Merthiolate into the nictitating membrane, although innumerable petechiae occurred with these agents.

13. Serum, heparin plasma, and citrate plasma, from rabbit origin, produced white emboli and petechiae following local injection in the nictitating membrane. With the exception of citrate plasma, petechiae were always produced. The latter appeared to diminish petechial formation and also the appearance of white emboli, both of which were lacking in the nictitating membrane of one animal but present in the four membranes of two other animals.

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AN INTERPRETATION OF THE INCIDENCE OF MURAL THROMBI IN THE LEFT AURICLE AND APPENDAGE WITH PARTICULAR REFERENCE TO MITRAL COMMISSUROTOMY

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RECENT developments in cardiac surgery have demonstrated the technical feasibility of mitral commissurotomy and its distinct value in selected cases of severe mitral stenosis.

A significant complication of this procedure is the occurrence of embolic phenomena, particularly to the brain, as noted in several recent reports.[1-3] Bailey and associates[4] report cerebral embolization in 5.1 per cent of their 235 surgical cases. Few accurate statistics concerning the source of these emboli are available because of the paucity of post-mortem studies which differentiate thrombi in the appendage from those in the auricle, and the frequent difficulty of recognizing clinically visceral embolization. The danger of cerebral embolization in these patients has stimulated several surgeons to use temporary compression of the carotid arteries during the period of intracardiac manipulation.[2-4] These facts emphasize the need for further information regarding the possibility of systemic emboli arising from the left auricle or its appendage during this surgical procedure, although these chambers may not be the only source of cerebral emboli.[4]

MATERIAL

During the years 1936 to 1950 inclusive, 8,676 autopsies were performed at the Queens General Hospital. Five hundred nine (5.9 per cent) of these were considered to be cases of rheumatic heart disease by fulfilling the following criteria: (1) fusion and retraction of the mitral or tricuspid valves; (2) fusion and shortening of the chordae tendinae; (3) noncalcific fusion of the aortic valve; (4) any fusion, including calcific changes, of the aortic valve when it was associated with definite rheumatic mitral valve involvement; (5) active rheumatic heart disease with Aschoff bodies or characteristic verrucae; (6) bacterial endocarditis of the mitral or aortic valves with some evident distortion, but the estimation of the severity of rheumatic damage being difficult.

The following cases were excluded from this study: (1) slight mitral changes (for example, tonguelike extensions of the valve cusps), or distortion which did not fulfill the criteria stated above (points 1 and 2); (2) slight aortic stenosis with or without slight mitral involvement; (3) calcific aortic stenosis with or without slight mitral changes; (4) calcification of the valve rings alone.

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Thus 103 cases of calcific aortic stenosis and seventy-two cases of doubtful origin were excluded from this series.

RESULTS

In 509 cases of rheumatic heart disease, thrombi were present in one or more cardiac chambers of 137 (26.9 per cent) patients. Thrombi occurred in the left auricle and/or the left appendage in 123 hearts (24.2 per cent); some of these also had thrombi in other chambers.

Of these 509 hearts, 296 (58 per cent) were considered to have moderately or markedly severe involvement of the mitral valve with or without associated calcification, and with or without disease of the other valves. They were selected because of their resemblance to cases chosen for mitral commissurotomy.

Of those cases showing severe mitral valve distortion, sixty-eight (23 per cent) were associated with ante-mortem thrombi in the left auricle, with or without thrombi in other chambers. Similar thrombi were present in the left appendage in sixty instances (20.3 per cent), with or without associated thrombi in other parts of the heart. A total of 106 cases (35.8 per cent) of severe mitral valve disease had thrombi in the left auricle and/or its appendage, with or without thrombi in the other chambers. These results are tabulated in Table I.

TABLE I.

	ANTE-MORTEM THROMBI IN					
	LEFT AURICLE		LEFT APPENDAGE		LEFT AURICLE AND/OR APPENDAGE	
	(NO.)	(%)	(NO.)	(%)	(NO.)	(%)
Severe mitral stenosis with or without other valve involvement	68	23.0	60	20.3	106	35.8
Severe mitral stenosis without severe aortic valve involvement	40	13.5	29	9.8	55	18.6

In order to further approximate the cases chosen for mitral commissurotomy, these calculations were repeated after excluding hearts showing severe mitral valve disease with associated severe involvement of the aortic valve.

Thus thrombi were present in the left auricle in forty (13.5 per cent) of these hearts, and in the left appendage in twenty-nine (9.8 per cent) hearts, with or without thrombi in the other chambers. In fifty-five instances (18.6 per cent) of severe mitral valve distortion without associated severe aortic valve involvement, there were thrombi present in the left auricle and/or its appendage. These results are tabulated in Table I.

COMMENT

Although these cases were chosen only on the basis of severe valvular involvement without regard to the age of the patient, the presence of auricular

fibrillation, the severity of congestive heart failure, or consideration of other criteria used in the selection of patients for mitral commissurotomy,[1,2] the results still offer the surgeon an estimate of the likelihood of encountering thrombi in the left auricle or appendage and the possibility of dislodging them while traversing these chambers.

These figures indicate that removal of clot from the left appendage before entering the auricle will materially reduce the frequency of thrombus which is available for embolization (from 18.6 per cent to 13.5 per cent). However, operation performed solely for the purpose of ligating[5] or amputating[6] the auricular appendage would hardly seem worthwhile since the left auricle contains thrombi approximately as often as the left appendage. Similar conclusions have been drawn by Jordan and associates.[7]

Since thrombi in the auricle itself are more difficult to recognize at the time of operation, it is important for the surgeon to appreciate the danger of dislodging clots from this chamber. As thrombi in the left auricle are usually on the posterior and lateral walls, the risk of embolization may be diminished by avoiding this area as much as possible as well as by compression of the carotid arteries.

This analysis also indicates that a higher incidence of mural thrombi in these chambers may be expected when the criteria for mitral commissurotomy are extended to include cases with more severe aortic involvement. The explanation of these results is being presented separately.

It is of interest that the recent immediate mortality figures for this operation are considerably less than the incidence of mural thrombi found in this study. It may be presumed that in many cases embolization does not occur, or usually affects tissues where infarction produces few or no clinical symptoms.[4] These factors are being subjected to further study.

SUMMARY AND CONCLUSIONS

1. The incidence of mural thrombi in the left auricle and the left appendage in 296 cases of severe mitral stenosis studied at autopsy is reported.

2. The application of these findings to the field of cardiac surgery for rheumatic heart disease is discussed.

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FLICKER FUSION NITROGLYCERIN TESTS IN NORMAL YOUNG ADULTS

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THE FREQUENCY at which flashes of light appear to fuse into continuous illumination is called the fusion frequency of flicker, or the flicker fusion threshold. This threshold is measured under standard conditions by a flicker photometer.[1] It is depressed with advancing age,[2] fatigue of the central nervous system,[3] high altitude,[1] hypothyroidism,[4] anemia,[3,5] circulatory insufficiency,[5] and probably by any factor causing debilitation or ease of fatigue. Because it is consistently depressed by circulatory failure, anemia, and rarefied atmospheres the reaction is believed to be due to anoxia of the visual tracts.

Krasno and Ivy[1] studied the effect of nitroglycerin on the flicker fusion threshold in patients. They assumed as a working hypothesis: (1) that the anoxia of the visual tract is due largely to spasm of the retinal arteries; (2) that there exists an intimate relation between the embryologic development and the vasomotor supply of the heart and retina and that, therefore, vasospasm in the latter might reflect a similar condition in the former; (3) that because diffuse vascular disease, especially hypertension, is frequently accompanied by changes in the retinal arteries there probably is hypertonus or spasm of these arteries for an appreciable period prior to the development of frank hypertension; (4) that the retinal spasm could be released by nitroglycerin with resulting improvement in the flicker fusion threshold, and (5) that in the normal subject the administration of nitroglycerin would cause dilatation of the retinal arteries resulting in passive congestion of the retina which in turn would either depress or not significantly change the flicker fusion threshold.

To investigate the validity of their assumptions Krasno and Ivy devised the flicker fusion nitroglycerin test which consists essentially in determining the flicker fusion threshold under standard conditions, then administering sublingually 0.4 mg. of nitroglycerin and immediately determining the flicker fusion threshold every two minutes for a period of six minutes. This is known as the "single test." The "double test" involves immediately repeating the sublingual nitroglycerin and again determining the flicker fusion threshold every two minutes for a period of six minutes.

A normal response was defined as a threshold depression after nitroglycerin of sixty or more flashes per minute. An abnormal response was defined as an elevation of the threshold of sixty or more flashes per minute. If nitroglycerin

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failed to alter the threshold as much as sixty flashes per minute in either direction the reaction was spoken of as "no change." The double test was performed whenever there was a no change response to the single test.

Krasno and Ivy studied the flicker fusion nitroglycerin test response of patients with and without evidence of cardiovascular disease. They did not publish any observations on normal subjects. They concluded that the flicker fusion nitroglycerin test may, by detecting retinal arterial spasm, prove to be a valuable aid (1) in the detection of angina pectoris and coronary occlusion, (2) in the appraisal of the therapeutic effect and determination of the optimal dosage of vasodilator drugs, and (3) in the selection from a group of apparently normal people those individuals likely to develop hypertension and/or coronary artery disease later in life.

The working hypothesis of Krasno and Ivy is based on the assumption that nitroglycerin will alter the flicker fusion threshold uniformly and consistently enough to distinguish normal from abnormal or potentially abnormal people. These assumptions are based on observations of patients, but lack supportive data obtainable from a study of normal subjects. It seems probable that nitroglycerin will affect a patient even though mildly debilitated differently than it will a normal subject. Results obtained from patients even though they show no evidence of cardiovascular disease should, therefore, not be used to establish a normal pattern.

At the time of publication of Krasno and Ivy's paper no information was available about the distribution pattern for the test in normal subjects. Our study was therefore designed, in part at least, to establish this basic pattern. Because of the relative freedom of young adults from disease we selected our subjects from student nurses and junior college students.

Prior to the conduction of the flicker fusion nitrogylcerin test a complete medical history and a thorough physical examination, including a careful funduscopic examination, was done by one of us (R.E.J. or M.C.K.) on each prospective subject. All students showing evidence of any type of disease were excluded from the study. Two hundred fifty students ranging in age from 17 to 25 years (average 20 years) qualified as normal.

The specifications of Krasno and Ivy for the standard conditions and for the performance of the flicker fusion nitroglycerin test were strictly followed. All tests were performed by one of us (R.E.J. or M.C.K.). The nitroglycerin employed was obtained from a fresh supply and was kept in tightly stoppered glass bottles. Table I provides a tabulation of data obtained from the two hundred fifty normal subjects.

RESULTS

Forty-one (16.4 per cent) of the two hundred fifty subjects showed an "abnormal" response to either the "single" or "double" flicker fusion nitroglycerin test. These subjects were retested fourteen to twenty-eight days later. Each subject was again examined to exclude infection, exhaustion, or other factors which might influence the test. If any of these factors were suspected, the subject was retested at a later date. Of the forty-one subjects initially found positive, only twenty-seven were positive to the final test. These twenty-seven subjects

TABLE I. DATA OBTAINED FROM 250 NORMAL SUBJECTS

Age range:	17 to 25 years	Average age:	20 years
Sex Distribution:	Men 110	Women 140	
Number of subjects with positive F.F.N.G.T. (initial test):			41
	Men 12	Women 29	
Number of subjects with positive F.F.N.G.T. (final test):			27
	Men 8	Women 19	
F.F.T. range of entire group:	2,400 to 3,000 flashes/minute		
Average F.F.T. of entire group:	2,640 flashes/minute		

F.F.N.G.T. = Flicker fusion nitroglycerin test.
F.F.T. = Flicker fusion threshold.

were then submitted to a battery of diagnostic studies including routine urinalysis, hemoglobin, complete blood count, fasting blood sugar, blood urea, blood cholesterol, pulmonary roentgenogram, electrocardiogram including standard leads, unipolar limb leads, V_R V_L V_F, and precordial leads V_1 to V_6, inclusive. Table II summarizes the diagnostic studies accumulated on the twenty-seven subjects. It will be noted that all results are well within normal limits.

DISCUSSION

According to the criteria of Krasno and Ivy our findings indicate that forty-one of the 250 normal subjects could be expected to develop coronary artery disease and/or hypertension. This seemed an appalling number of candidates in so young an age group. In order to obtain more definite information concerning this phase of the problem, we consulted Mr. Louis Dublin, chief statistician for the Metropolitan Life Insurance Company who made available the statistics of Theodore D. Woolsey.[6] These were used as a standard by which to judge the plausibility of our findings. Woolsey's statistics indicate that only 3.6 per cent of the men and 4.7 per cent of the women at 20 years of age can be expected to develop hypertension or heart disease (all types) by the age of 40. The results of our tests show an expected incidence of coronary artery disease plus hypertension of 10.9 per cent in men and 20.7 per cent in women.

It is almost inconceivable that we could have selected from our 250 normal subjects every individual who, during the next twenty years, would develop hypertension and/or coronary artery disease. Assuming, however, that all potentially abnormal subjects were selected, then Woolsey's statistics reveals that for each accurately selected man and woman we would, in addition, have erroneously selected two men and three women. These figures indicate that a positive response to the flicker fusion nitroglycerin test occurs far too frequently, at least in this age group, to be useful in detecting those apparently normal individuals who will develop hypertension and/or coronary artery disease during the next twenty years.

To be of value in appraising the therapeutic effect and determining the optimal dosage of vasodilator drugs, the test data furnished should be constant under standard conditions. Of the forty-one subjects initially found positive, only twenty-seven were positive when retested. Had we administered vasodilator drugs or in fact any therapeutic regime to the forty-one initially positive

TABLE II. SUMMARY OF STUDIES ON THOSE SUBJECTS POSITIVE ON THE INITIAL AND FINAL F.F.N.G.T.

SUBJECT	AGE (YEARS)	SEX	HEIGHT (INCHES)	WEIGHT (POUNDS)	R.B.C. (mil/c.mm.)	HGB. (%)	F.B.S. (MG. %)	CHOLESTEROL (MG. %)	BLOOD UREA (MG. %)	F.F.T. FL./MIN. (FINAL)	INCREASE F.F.T. FL./MIN. AFTER NITROGLYCERIN
1. M. D.	23	F	65	130	4.76	90	93	184	30	2760	150
2. B. G.	21	F	64	118	4.20	84	92	150	24	2700	120
3. D. G.	21	F	64	117	4.27	85	90	180	25	2640	120
4. M. C.	19	F	61	130	4.60	96	91	190	21	2700	120
5. A. V.	22	F	63	130	4.00	82	95	150	21	2700	120
6. J. S.	20	F	67	135	4.60	90	81	220	24	2600	120
7. B. M.	22	F	60	134	4.70	94	80	200	36	2640	180
8. D. K.	19	F	67	130	4.40	88	91	175	22	2640	120
9. I. S.	21	F	62	145	4.06	84	93	230	25	2820	90
10. M. G.	20	F	62	142	4.20	84	105	140	34	2820	180
11. B. G.	19	F	62	123	4.40	90	97	175	23	2800	160
12. G. G.	21	F	65	138	4.27	81	84	230	20	2700	120
13. B. D.	20	F	63	125	4.40	84	95	230	21	2610	150
14. O. G.	20	F	68	141	4.00	82	88	150	20	2700	120
15. R. H.	22	M	70	158	4.50	95	97	210	30	2580	120
16. E. F.	21	M	70	165	4.90	96	83	155	30	2550	150
17. L. B.	18	M	69	163	4.60	88	98	150	33	2700	180
18. R. S.	18	M	67	157	5.30	102	102	180	34	2940	120
19. L. R.	23	M	68	170	5.20	100	85	200	27	2670	150
20. T. C.	18	M	67	150	5.00	95	85	230	26	2760	180
21. E. W.	18	M	68	160	5.40	106	81	155	30	2820	180
22. D. T.	18	M	69	150	5.00	96	95	210	35	2760	120
23. B. C.	18	F	61	120	4.64	85	92	180	33	2550	150
24. J. D.	18	F	62	129	4.48	86	100	205	31	2610	150
25. M. T.	17	F	63	139	4.96	89	90	180	30	2640	120
26. J. W.	19	F	63	120	4.64	86	103	190	23	2700	120
27. R. C.	18	F	64	125	4.96	91	80	220	24	2760	120

Urinalysis, electrocardiogram, and pulmonary roentgenogram were normal for all twenty-seven subjects.
F.F.T. = Flicker fusion threshold.
F.B.S. = Fasting blood sugar.
R.B.C. = Red blood cell count.

subjects, we could have claimed release of retinal spasm in fourteen subjects and erroneously credited the regime with excellent therapeutic possibilities. This lack of uniformity of test data obtained in normal subjects disqualifies the test as a useful method of measuring the effect of vasodilator drugs.

STATISTICAL ANALYSIS

An adequate test for differentiating between normal and abnormal subjects should furnish test response data which can be distinctly separated into two categories with very little or preferably no overlap. If the test has wide variability the distribution of the extreme values is of far greater importance than the averages. Many treatments of test response data are based on symmetrical or even normal (gaussian) distributions. Here the probability of obtaining low values and high values is the same. The occurrence of more extreme values on one side of the distribution than on the other may be of significance in the possible overlap region between normal and abnormal subjects.

Plotted curves of the data obtained from men and women show that there is no inherent difference in their response. The data from both sexes was therefore combined to give a larger sample from which to establish the proper distribution pattern. A scatter plot showed that there was no relation between the flicker fusion threshold before nitroglycerin and the change in the threshold caused by nitroglycerin. A plot of the cumulative percentages on probability paper showed that there is no evidence of two separate distributions since the values below and above +60 are obviously part of the same distribution which is, however, not symmetrical.

Table III shows an analysis of the results obtained from the 250 subjects tested. Eighty-three and six-tenths per cent are within the Krasno-Ivy normal range response to nitroglycerin (−60 to +59). Sixteen and four-tenths per cent show an elevation of the flicker fusion threshold after nitroglycerin of sixty or more flashes per minute and are therefore abnormal according to the Krasno-Ivy criteria. There are more values above +60 than below −60. Thus, responses of

TABLE III. ANALYSIS OF TESTS DONE ON 250 NORMAL SUBJECTS

	F.F.N.G.T. RESPONSE	NUMBER OF SUBJECTS			PER CENT OF TOTAL
		MEN	WOMEN	TOTAL	
Normal Range	−60 to +59	98	111	209	83.6
	+60	2	3	5	2.0
	+90	2	8	10	4.0
Abnormal Range	+120	6	14	20	8.0
	+150	1	1	2	0.8
	+180	1	3	4	1.6
Total Abnormals		12	29	41	16.4

+60 and above are a natural consequence of the test in these normal subjects. Values of +150 and above, for example, occurred 2.4 per cent of the time. Conclusions based on a symmetrical distribution curve would, because of the asymmetry of the actual distribution, be considerably in error.

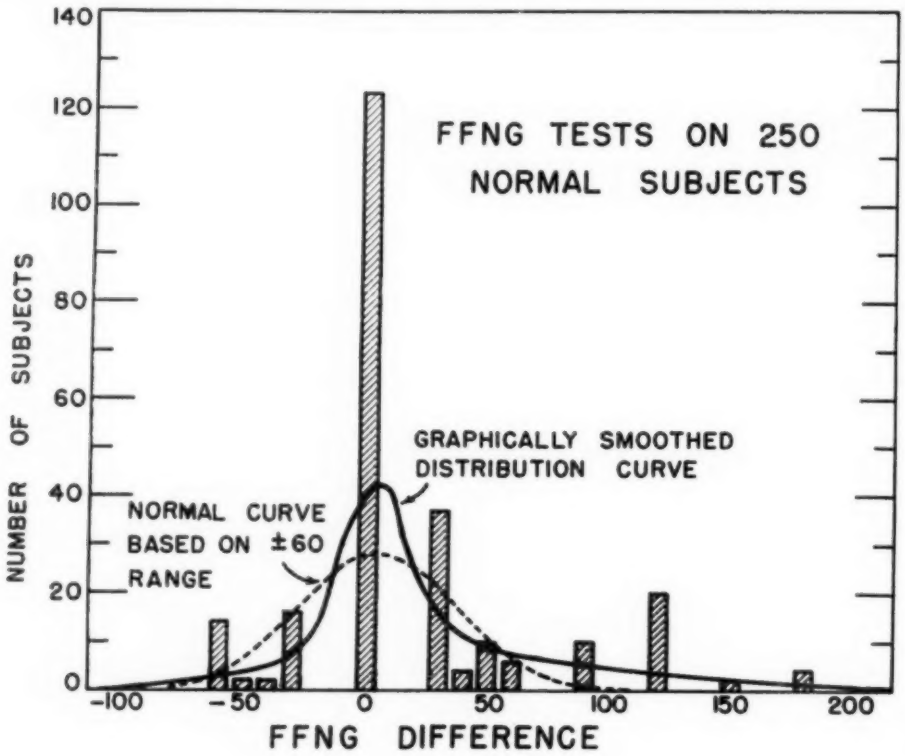

Fig. 1.

Fig. 1 shows a comparison of the observed distribution with a normal (gaussian) distribution curve based on the values obtained from our subjects within the Krasno-Ivy normal range (for convenience the +60 and −60 values were included). In this way the high values at +90 to +180 were excluded. A special technique devised by Cohen[7] permits the whole of the normal distribution curve to be estimated even when part of one of the ends or tails is missing, in this case the part above +60. The result of this calculation showed that only about 3 per cent (seven) of the values should, on this assumption, be above +60 and that the standard deviation should be about thirty-two flashes per minute. When considered as a whole, it is obvious that this is an unrealistic picture of the present measurements. While the ±60 range is adequately enough represented the large number of values (thirty-six) above +60 actually present is badly underestimated. The high variability of response is also emphasized by the repeat tests in which only twenty-seven of the forty-one subjects were again abnormal.

Comparison of the initial and final flicker fusion nitroglycerin test response in the forty-one subjects found positive to the initial examination is given in

TABLE IV. COMPARISON OF INITIAL AND FINAL F.F.N.G.T. RESPONSE IN THE FORTY-ONE SUBJECTS FOUND POSITIVE TO THE INITIAL EXAMINATION

NUMBER OF SUBJECTS	INITIAL TEST	FINAL TEST	DIFFERENCE
5	+60	0	−60
1	+90	0	−90
3	+90	+30	−60
4	+90	+120	+30
2	+90	+150	+60
1	+120	−30	−150
2	+120	0	−120
1	+120	+30	−90
1	+120	+90	−30
8	+120	+120	0
5	+120	+150	+30
2	+120	+180	+60
1	+150	+30	−120
1	+150	+180	+30
2	+180	+120	−60
2	+180	+180	0

Table IV. This data demonstrates that the lack of reproducibility of the test on the same subject may be a significant factor in the widely variable results obtained. However, it is not possible from our present data to differentiate between test-to-test variability on the same subject and test response variability in different subjects. Forty-one subjects on whom we repeated the flicker fusion nitroglycerin test showed a prenitroglycerin threshold range of only ten to sixty flashes per minute. The postnitroglycerin thresholds, however, varied from 30 to 150 flashes per minute. The wide variation in the postnitroglycerin threshold is obviously due to the inconstant effect of nitroglycerin. It seems possible that nitroglycerin, because of its powerful action and its multiple influences, produces a complicated circulatory situation which may vary rapidly and widely in different subjects or in the same subject at different times. It does not seem surprising then that a high percentage of inconstant and erratic results may be obtained even under the most carefully controlled circumstances.

The 250 results indicate that the underlying distribution is inherently skewed or lopsided with a high degree of variability and that the abnormal values obtained are a perfectly natural response of normal healthy subjects. Thus, high values do not necessarily indicate abnormal or potentially abnormal states.

The study by Keys and Simonson[8] on normal subjects and on subjects with known cardiovascular disease confirms these conclusions in another way. For fifty-eight seated normal men, the average flicker fusion nitroglycerin test difference was +8 flashes per minute with a standard deviation of fifty-two flashes per minute. For thirty-five seated men with hypertension the average flicker fusion nitroglycerin test difference was +10 flashes. The variability in the latter group, however, was approximately twice as high, since the standard deviation was +111 flashes per minute. While it is impossible to interpret their data in an absolute sense without knowledge of the underlying distribution it is obvious that the two distributions not only overlap but essentially fall on top of each other. Their study indicates, therefore, that a large percentage of normal people are abnormal and that a large number of patients with known cardiovascular disease are normal.

SUMMARY

The flicker fusion nitroglycerin test was performed on 250 normal adults ranging in age from 17 to 25 years, and averaging 20 years.

The results of the tests are discussed. A statistical analysis is used to emphasize the erratic nature of the findings.

It is suggested that nitroglycerin produces such a complicated circulatory situation encompassing so many variables that inconstant and erratic results are the natural consequence.

This lack of uniform results obtained under standard conditions precludes reliance on the test in the study of vasodilator drugs and in the selection, at least in this age group, of those apparently normal persons likely to develop hypertension and/or coronary artery disease in the next twenty years.

We are greatly indebted to Mr. George Thomson, Ethyl Corporation Research Laboratories, for his statistical analysis of the present data, and to Franklin D. Johnston, M.D., University of Michigan, for the oscillographic confirmation of the accuracy of the flicker photometer used in these studies.

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A MODEL WHICH DEMONSTRATES THE QUANTITATIVE RELATIONSHIP BETWEEN THE ELECTROMOTIVE FORCES OF THE HEART AND THE EXTREMITY LEADS

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MODELS of various types have frequently been employed to illustrate or explain the manner in which the electrical activity of the heart gives rise to the indirect electrocardiographic leads. Thus, Einthoven and associates[1] schematized the human body into a flat, equilateral triangular, electrically homogeneous volume conductor with the electrical activity of the heart represented as a vector at the center of the triangle. Craib[2] treated the body as a homogeneous, spherical volume conductor with an electrical dipole at the center of the sphere. Employing a plane circular tank filled with frog Ringer's solution, Eyster, Maresh and Krasno[3] compared the potentials produced at the periphery of the tank by a centric dipole with those generated by a beating frog heart immersed at the center of the tank. Katz[4] also studied the potential and streamline distribution of the electrical field produced by a centric dipole within a flat, circular volume conductor. He then demonstrated the departures from this relatively simple situation produced by such factors as irregularity of the tank shape, eccentricity of the dipole placement, odd shapes of the pole electrodes and electrical inhomogeneities in the volume conductor.

All of the preceding work has been concerned solely with the distribution of electrical current and potentials arising from internal sources and sinks. Application of the principle of reciprocity to electrocardiographic theory makes it equally important, and perhaps more illuminating, to study electrical fields which are generated by current flowing through the model by way of external electrodes. The analysis of such externally (reciprocally) energized fields leads to the development of simple laws which accurately quantitate the relationships between the various electrocardiographic leads and the cardiogenic currents which produce them. McFee and associates[5] have recently reported on a hydraulic model which demonstrates the streamlines of reciprocal fields in a qualitative manner. It is the purpose of the present communication to describe electrical models, recently devised in this laboratory, in which the properties of reciprocal fields can be quantitatively determined. The determination of these properties made it possible to establish laws for the magnitudes of the extremity leads which were confirmed by experimental observations.

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THEORETICAL CONSIDERATIONS

If a volume conductor is energized with a current, i, through one pair of electrodes, a potential difference, E, may be measured across a second pair of electrodes. Conversely, according to the principle of reciprocity,[6] if the second pair of electrodes is energized with the same current, i, the potential difference developed across the first pair of electrodes will be exactly E. This property of volume conductors can be applied advantageously in establishing the relationships of dipole sources within the model to the magnitude of potential differences between pairs of extremity electrodes. The rationale consists of determining the laws of the potential difference between two closely spaced points within the model when the model is reciprocally energized through pairs of extremity electrodes. The same laws will then express the potential difference across pairs of extremity electrodes when the two points are employed as a point source and sink of electricity.

If two points in the reciprocally energized field are close enough to each other that the gradient* of the field in the vicinity of the points is virtually uniform, the potential difference between the two points may be expressed as

$$PD = |\text{grad } E_r|\ d \cos \phi \quad (1)$$

where PD is the potential difference between the two points, grad E_r is the gradient of the reciprocal field, d is the distance between the two points and ϕ is the angle between the gradient and a line joining the two points. If the reciprocal field had been generated by a standard current of, say, 1 milliampere, a current of i milliamperes flowing in and out of the two points as point source and point sink will generate a potential difference across the electrodes by which the model was reciprocally energized equal to

$$PD = |\text{grad } E_r|\ id \cos \phi \quad (2)$$

We may employ the simpler and more powerful vector notation

$$PD = \text{grad } E_r \cdot \mathbf{E}_m \quad (3)$$

where $\mathbf{E}_m$ is a vector of magnitude id (moment of the dipole) and having the direction of the line passing through the two points (axis of the dipole).

It is apparent from equation 3 that the magnitude of an Einthoven lead resulting from a closely spaced point source and sink (electric doublet) within the model is the dot (or scalar) product of two vectors. One of the vectors is the gradient produced in the vicinity of the doublet by reciprocally energizing the lead with one unit of current. The other vector, called $\mathbf{E}_m$ to conform to the concept of manifest potential introduced by Einthoven and associates,[1] has as its magnitude the moment of the doublet and as its direction the axis of the doublet. The magnitude of the lead can therefore be predicted if its parent vectors are

*The gradient of an electrical field is a vector point function of the field which describes the magnitude and direction of the maximum rate of potential increase at any point in the field. Its direction is normal to the isopotential line which passes through the point. It may be expressed mathematically for a two-dimensional field as:

$$\text{grad } E = \mathbf{i}\, D_x E + \mathbf{j}\, D_y E$$

where $\mathbf{i}$ and $\mathbf{j}$ are the unit positive vectors in the horizontal and vertical directions, respectively, and $D_x E$ and $D_y E$ are the corresponding rates of potential change in the horizontal and vertical directions.

known. In the models, the values of the manifest potentials are determined by fiat. The determination of the gradients of reciprocal fields is more difficult. In simpler cases, such as a model consisting of a flat, circular, homogeneous volume conductor with point electrodes on the periphery, we have been able to calculate the gradients of the reciprocal fields from theoretical considerations. In the more complicated types of models, such as are to be described in this paper, it is necessary to determine the gradients of the reciprocal fields by experimental means.

METHODS AND MATERIALS

We constructed a series of two dimensional models of human form from sheets of type 1 Teledeltos paper,* an electrically conducting material of intermediate resistivity. Areas of increased conductivity were produced by superimposing one or more layers of desired shape on the basic model. Electrodes were painted with silver ink† at the ends of both upper extremities and at the end of the left lower extremity. The mechanical and electrical bonding of superimposed layers of the Teledeltos paper to the basic pattern of the model required considerable care, but after some practice it was accomplished without too much difficulty. Small amounts of silver ink were added to a quantity of amyl acetate until a mixture was achieved which possessed the following uniquely desirable properties. When the mixture was painted on a nonconducting surface and permitted to dry, the resistance between two points on the film a few centimeters apart was on the order of 100 megohms. The resistance through the thickness of the same type of film, as measured between its surface and a conductor upon which it had been painted, was virtually zero. A small quantity of polystyrene coil dope‡ was added to this mixture to replace some of the "body" which was lost in the dilution of the ink.

A piece of photographic dry mounting tissue,§ cut to leave a free margin of approximately 1 cm. width, was applied to the back of the sheet which was to be bonded to the basic model. The insulating backing of the Teledeltos paper was wiped away from this free margin with a cotton sponge moistened with amyl acetate. The sheet, thus prepared, was placed on the basic model in the desired location and mechanically bonded to it by means of a hot flat-iron. Using the modified silver ink preparation described above as a cement, the free margins of the superimposed layer were bonded to the basic layer. Because of the unique resistance properties of this preparation the superimposed sheet was electrically bonded at its margins to the basic pattern without increasing the conductivity in the marginal areas beyond that of a sheet of double thickness. It was necessary to achieve electrical bonding only in the marginal areas since a theoretical and experimental analysis indicated that the lines of electrical flow divided themselves equally between the two sheets within a distance of less than 1 mm. from the edge of the superimposed layer. Therefore the dry mounting tissue was employed everywhere except in the marginal areas in order to mechanically

*General Electric Company.
†Silver Print, No. 21-2, General Cement Manufacturing Company.
‡General Cement Manufacturing Company.
§Eastman Kodak Company.

strengthen the union between the two sheets. The same principles applied to the superposition of a third layer upon the model.

A dipole was constructed by mounting two electrodes 1 cm. apart through a sheet of Lucite. The ends of the electrodes terminated in conical points. A third, rounded, rod was also mounted in the sheet of Lucite to provide a tripod base for the assembly. Stability of position and good electrical contact was insured by placing a small weight on top of the Lucite sheet. The electrodes could either be energized with electricity to act as a source dipole or they could be used as a detector dipole to determine the potential difference between them in a reciprocal field.

Three models made to a 1:2 scale from a man 74 inches (188 cm.) tall and of average bodily habitus were studied in detail. They consisted of

Model No. 1, two layers of Teledeltos paper
Model No. 2, same as No. 1, but the areas corresponding to the lungs cut out of the upper layer
Model No. 3, same as No. 2, but a third layer corresponding to the areas of the heart, great vessels and abdominal viscera superimposed.

In general, three types of observations were made on the models: (1) isopotential distribution of the reciprocal fields, (2) determination of the gradients (lead vectors) of the reciprocal fields and (3) measurement of the extremity leads when the model was energized with a cardiac dipole of known manifest potential. The isopotential distributions were plotted by a low frequency (120 cycles per second) resistance bridge technic in which the model comprised two arms of the bridge. A high-sensitivity vacuum tube voltmeter was employed as the null detector. The other measurements were made with direct current energization of the model. Potentials were measured with a potentiometer of medium precision.*

RESULTS

Isopotential Distribution.—In Fig. 1, *A*, *B*, and *C*, the isopotential distribution resulting from the reciprocal energization of Lead II in each of the three models is shown. The respective gradients at a point corresponding to the septum of the heart near its base (point *B*) are also depicted. The Lead II vectors can be roughly estimated from an inspection of these isopotential plots on the basis that the vectors are directed normally to the isopotential lines and their magnitudes are inversely proportional to the spacing between the isopotential lines. In Model 1 (Fig. 1, *A*) the isopotential lines are almost rectilinear in the vicinity of points *A*, *B* and *C*, and it may be anticipated that the lead vectors at these three points will be approximately equal in direction and magnitude. In the other two models the isopotential lines curve in the vicinity of the three reference points and the spacing between them changes. Therefore the lead vectors will be different from each other at the three points of reference. If the Einthoven triangle were valid for the models, even as a frame of reference, it would be necessary that the isopotential lines of the reciprocal field of Lead II be rectilinear

*Leeds and Northrup, Model No. 7655.

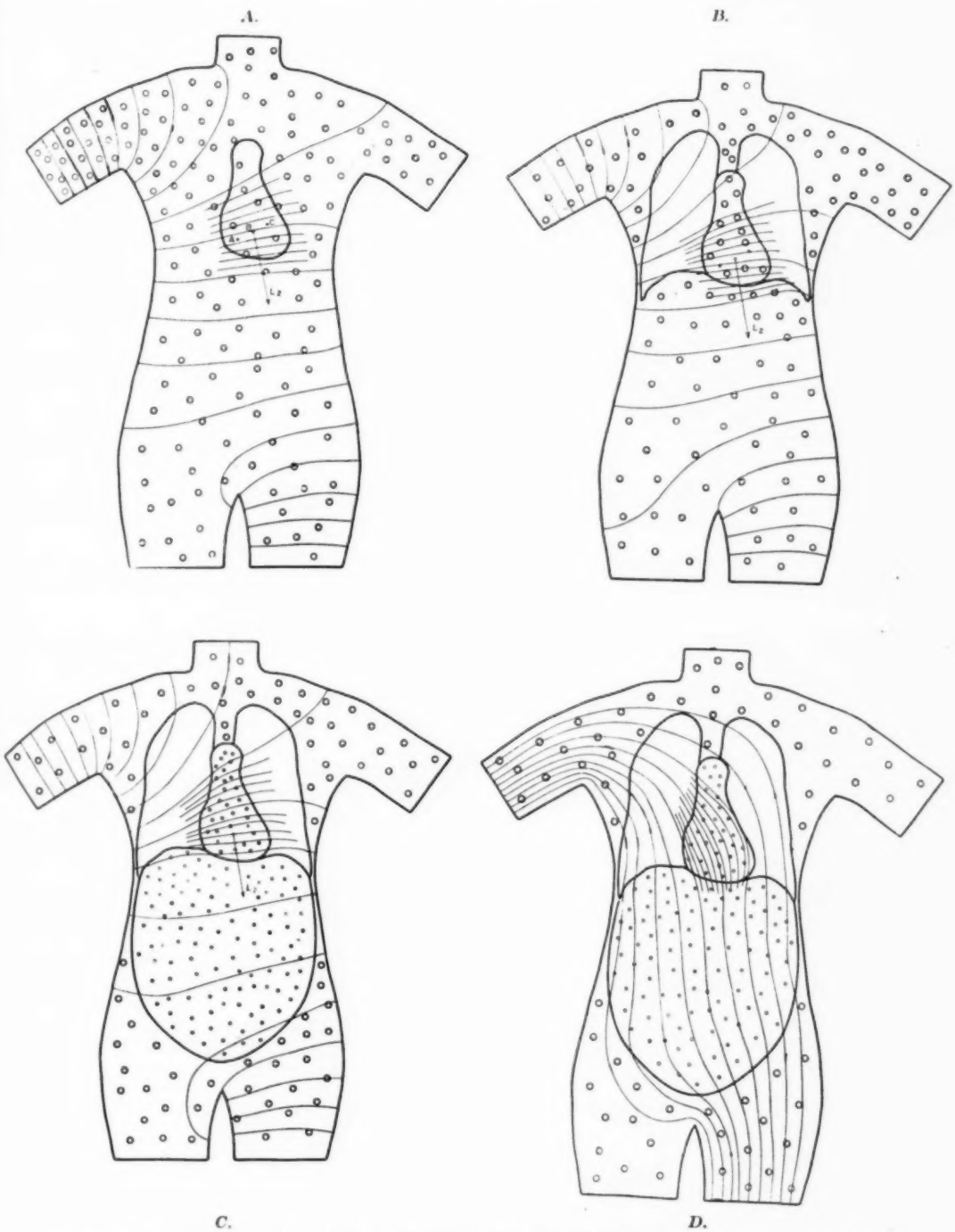

Fig. 1.—Reciprocal fields of the models energized through the Lead II electrodes. *A* to *C* show the isopotential distribution for Models 1 to 3, respectively. *D* shows the isoflow distribution (tubes of influence) for Model 3. Plain areas represent a model thickness of one sheet (conductivity = 1). Coarsely stippled areas represent two sheets (conductivity = 2), and the finely stippled areas, three sheets (conductivity = 3). Points *A*, *B*, and *C* are taken as being fairly representative of the right ventricular, septal and left ventricular regions, respectively. $\mathbf{L}_2$ is the Lead II vector for each model at point B.

in the cardiac vicinity and directed 30 degrees counterclockwise to the horizontal axis. It is apparent from inspection of the figures that this relationship does not exist in the models.

Lead vectors.—In each of the three models Leads I, II and III were reciprocally energized with 1 milliampere of direct current and the corresponding lead vectors determined at points *A*, *B*, and *C*. The technique of measuring the lead vector at a given point consisted of measuring the potential difference between two points ½ cm. to either side of the point on both its horizontal and vertical axes. These values constituted the mean horizontal and vertical components, respectively, of the lead vector in the vicinity of the point. The lead vector was computed by adding these two components vectorially.

Since the Einthoven law (I + III = II) is valid regardless of the manner in which electrocardiographic potentials are generated[7] it may be predicted that the vectorial sum of the Lead I vector ($\mathbf{L}_1$) and the Lead III vector ($\mathbf{L}_3$) will equal the Lead II vector ($\mathbf{L}_2$). This relationship may be depicted graphically by plotting $\mathbf{L}_1$ and $\mathbf{L}_2$ as arising from the same origin, and $\mathbf{L}_3$ as arising from the tip of $\mathbf{L}_1$. If the analysis is correct, and the lead vectors have been accurately determined, the plot of the three vectors should form a closed triangle. The lead vector data, plotted in Fig. 2, indicate that this relationship holds within the limits of experimental error.

The lead vectors determined from the models in this manner are approximately equivalent to the lead vectors calculated by Burger and van Milaan from their models.[8,9] Physically the lead vector at a point is identical to the gradient of the reciprocal field at that point. The triangular plot of the three lead vectors, known as a Burger triangle, is helpful since one can make a rough estimate of the relative magnitude of the Einthoven leads from it. Each lead will be directly proportional to both the projection of the manifest potential on the corresponding side of the Burger triangle and to the length of the side itself. The Einthoven triangle originally consisted of a flat, equilateral triangular schematization of the human body.[1] Subsequently, it has come to be regarded as a frame of reference for expressing the relationships between the manifest potential and the magnitudes of the Einthoven leads.[10] In that sense it constitutes a special case of the Burger triangle. Conversely, the Burger triangle is a generalization of the Einthoven triangle.

Relationships of Electrocardiographic Potentials to Source Dipoles.—The relationships expressed by equation 3 were tested by measuring the potentials of the Einthoven leads when the dipole was employed as a doublet of known moment and axis in a region where the lead vectors had been previously determined. The values of the lead magnitudes thus obtained were compared with those calculated according to equation 3. A typical set of such data is presented in Table I. The correlation between the calculated and observed values appears to be satisfactory.

The relationships between the Einthoven leads and the source doublet may be demonstrated graphically by plotting a triaxial reference system (Fig. 3) in which the three axes correspond in direction to the lead vectors in the vicinity of

TABLE I. COMPARISON BETWEEN THE CALCULATED AND OBSERVED LEAD VALUES FOR AN ELECTRIC DOUBLET PLACED AT POINT B, MODEL NO. 1

$E_m = 0.738\underline{/45°}$	$L_1 = 26.8\underline{/-9.3°}$ $L_2 = 54.3\underline{/77.2°}$ $L_3 = 59.3\underline{/103.9°}$

LEAD	CALCULATED VALUES	OBSERVED VALUES
I	(0.738) (26.8) cos 54.3° = 11.6 mv.	12.0 mv.
II	(0.738) (54.3) cos 32.2° = 34.0 mv.	34.8 mv.
III	(0.738) (59.3) cos 58.9° = 22.6 mv.	22.8 mv.

the dipole. The spacing between the scale marks on each of the axes is inversely proportional to the length of the corresponding lead vector. For example, the scale mark representing a value of n millivolts on the Lead I scale would be plotted out a distance of kn/L_1 from the origin, where k is a proportionality constant and L_1 is the magnitude of the Lead I vector. Such a plot may be used in two ways: (1) the manifest potential is plotted as a vector of known length and direction, and perpendiculars dropped to the three axes will give the anticipated values of the leads and (2) the values of the leads are plotted on the three axes, and perpendiculars constructed from the axes at these points will meet at a point which determines the tip of the manifest potential. The magnitude of the manifest potential is determined by dividing its plotted length by the proportionality constant, k.

In Fig. 3 the lead values obtained experimentally have been plotted on the axes and the perpendiculars constructed. The perpendiculars form a small triangle, the size of which is an indication of the magnitude of experimental error since the three lines should meet at a point. A line drawn from the origin of the axes to the center of the small triangle represents the magnitude and direction of the manifest potential. In the experiment depicted in Fig. 3 the agreement between theory and observation was good, the values being: theoretical, $\mathbf{E}_m = 0.74\underline{/45.0°}$; experimental, $\mathbf{E}_m = 0.76\underline{/44.5°}$.

Unipolar Extremity Leads.—Experiments conducted with unipolar leads will not be described here because it is clear that such leads are simple combinations of portions of the Einthoven leads.[11] However, the true physical significance of such leads may be clarified by applying the principle of reciprocity and the idea of lead vectors to them. For example if an individual were reciprocally energized through a lead V_f connection, 1/3 of the current would pass through the Lead II pathway and another 1/3 through the Lead III pathway. The remaining 1/3 of the current would be "wasted" through the third arm of the resistor network. Two lead vectors would thus be established at any point within the individual, one of them being 1/3 $\mathbf{L}_2$ and the other being 1/3 $\mathbf{L}_3$. By the principle of superposition the lead vector of V_f would be

$$\mathbf{L}_{Vf} = 1/3\ (\mathbf{L}_2 + \mathbf{L}_3) \quad (4)$$

If the individual were reciprocally energized through an aVf connection, none of the current would be "wasted" and it would be split equally between the Lead II and III pathways. Thus the lead vector would be

$$\mathbf{L}_{aVf} = \tfrac{1}{2}(\mathbf{L}_2 + \mathbf{L}_3) \quad (5)$$

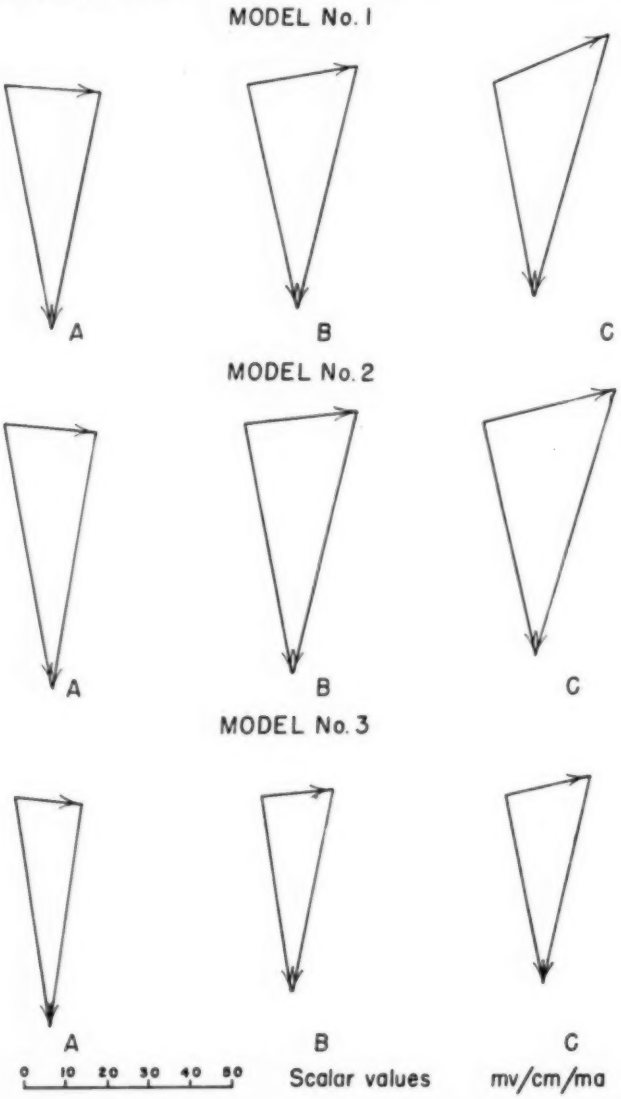

Fig. 2.—Lead vectors for points *A*, *B*, and *C* of each of the three models plotted in the form of Burger triangles. The "top" of each triangle is the Lead I vector, the "left" side is the Lead II vector, and the "right" side is the Lead III vector. Each set of vectors closes almost exactly, indicating a very small degree of experimental error.

Two conclusions regarding the relationships between these types of derived leads can be drawn from equations 4 and 5: (1) Their lead vectors are identically oriented and therefore the leads will have identical configurations except that (2) the magnitude of the augmented unipolar lead will be 50 per cent greater

than that of the corresponding Wilson unipolar lead. Failure to achieve these relationships in clinical electrocardiography[12] has been shown to result from incorrect lead connections.[13]

The lead vectors of the augmented unipolar extremity leads may be depicted graphically as the medians of the Burger triangle. $\mathbf{L}_{aV_R}$ is the median directed into the R corner of the triangle, $\mathbf{L}_{aV_L}$, into the L corner and $\mathbf{L}_{aV_F}$, into the F corner.

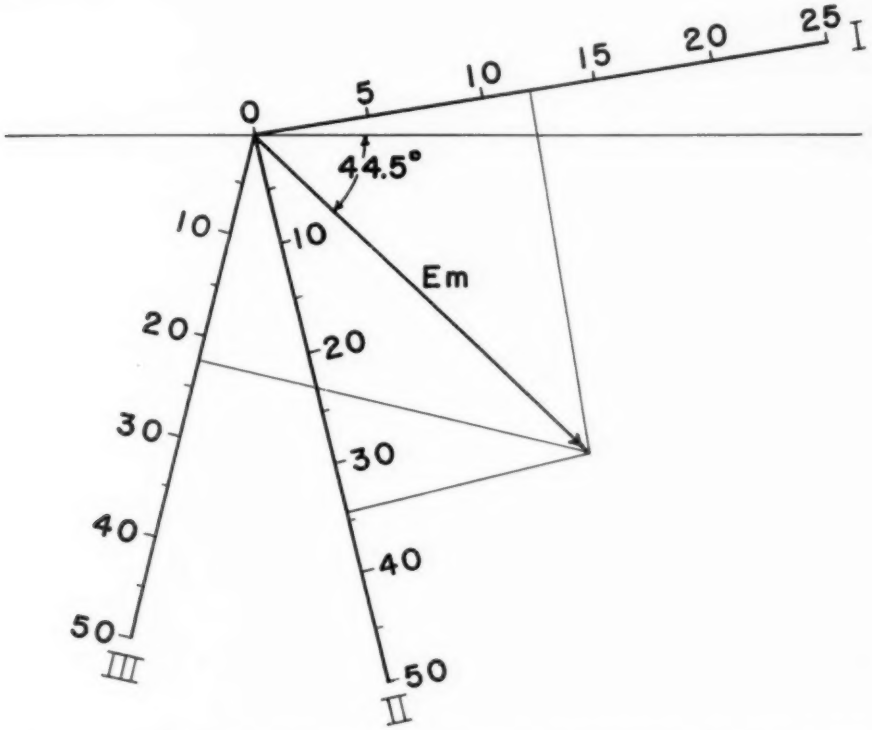

Fig. 3.—Generalized triaxial reference system fitted to the lead vector data for point *B*, Model 1. The perpendicular lines from each axis were plotted from experimental data obtained with the cardiac doublet oriented 45 degrees clockwise from horizontal. The three perpendiculars meet very nearly in a point, indicating a very small degree of experimental error.

The Burger triangle and its medians can be plotted as lead axes arising from a single origin. As was the case in the triaxial reference system (Fig. 3), each axis may be marked with a scale, the spacing between marks being inversely proportional to the magnitude of the corresponding lead vector. The resulting figure (Fig. 4) represents a generalization of the hexaxial reference system proposed by Graettinger and his associates.[14] Such a plot is somewhat more useful than the triaxial system since it includes the relationships between the manifest potential and the augmented unipolar extremity leads, and also the relationships between all of the various extremity leads.

The importance of thus "fitting" the triaxial and hexaxial reference systems to the lead vector data was demonstrated by plotting the lead values shown in Fig. 4 on the hexaxial plot of Graettinger and his associates. The manifest

potential determined in this manner had an apparent direction of 73 degrees as compared to a true value of 45 degrees. In contrast, the directional error in Fig. 4 is only a few tenths of a degree.

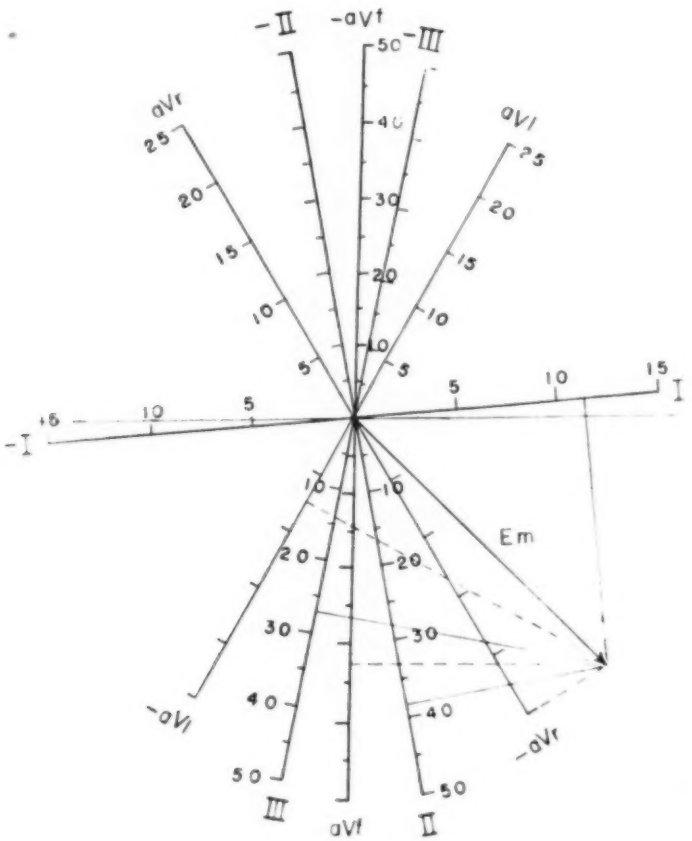

Fig. 4.—Generalized hexaxial reference system plotted from the Burger triangle and its medians for point *B*, Model 3. The solid perpendicular lines from the Einthoven lead axes were plotted from experimental data, determining the manifest potential as in Fig. 3. The dashed perpendicular lines were dropped from the tip of the manifest potential to each of the aV axes, thus determining the magnitude of the augmented unipolar leads.

Horizontal and Vertical Components of the Manifest Potential.—In order to record these components it is necessary to employ leads having vectors oriented horizontally and vertically, respectively. Such leads may be derived according to principles indicated in Fig. 5. In Fig. 5,*A*, the Lead I and Lead II vectors have been plotted as arising from the same origin. The triangle is completed with a line of length *d*. It may be shown by vectorial methods that a horizontal vector, $\mathbf{L}_H$, extending from the origin to the third side of the triangle consists of n parts of $\mathbf{L}_2$ and $1\text{-}n$ parts of $\mathbf{L}_1$, where n has the significance of proportionality indicated in the figure. In Fig. 5,*B*, the electrodes *L* and *F* of the model have been connected together with a resistor of magnitude r. A point, *P*, has been located on the resistor so that the resistance between *P* and *L* is nr, and that between *P* and *F* is

$(1\text{-}n)r$. Upon reciprocal energization between points P and R, $1\text{-}n$ parts of the current will flow through the Lead I pathway and n parts through the Lead II pathway. Therefore the lead vector for the pathway P to R will be identical to $\mathbf{L}_H$ and the potential differences recorded across P and R will be proportional to the horizontal component of manifest potential. A lead with a vertically oriented vector may be similarly derived.

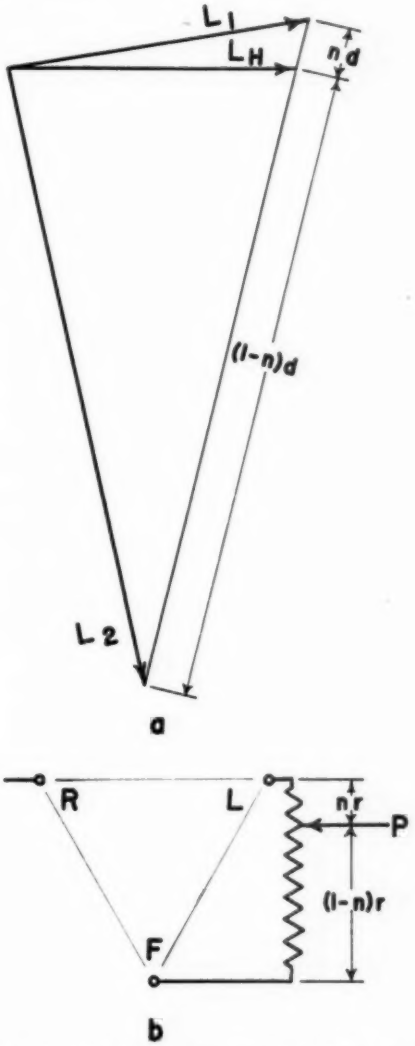

Fig. 5.—Illustration of the principles for forming a synthetic lead which has a horizontally oriented lead vector. The factor, n, ranges in value from 0 to 1, and is determined from the experimental data. The same principles may be employed to synthesize leads having any desired orientation of their vectors.

Using the principles outlined above we recorded the horizontal and vertical components of the cardiac dipole in the model. In order to improve the accuracy of our observations we included the resistances of the lead pathways in our calculations of nr and $(1\text{-}n)r$. A typical set of data is shown in Table II.

TABLE II. COMPARISON BETWEEN THE CALCULATED AND OBSERVED HORIZONTAL (E_H) AND VERTICAL (E_V) LEAD VALUES FOR AN ELECTRIC DOUBLET PLACED AT POINT B, MODEL NO. 1

$E_m = 1.48/45°$ $L_H = 25.3/0°$ $L_V = 54.8/90°$

LEAD	CALCULATED VALUES	OBSERVED VALUES
E_H	(1.48) (25.3) cos 45° = 26.4 mv.	26 mv.
E_V	(1.48) (54.8) cos 45° = 57.3 mv.	58 mv.

Tubes of Influence.—The streamlines of the reciprocal field of a lead have been referred to as tubes of influence[10] since, in homogeneous media, the effect of a wave of depolarization or repolarization on the particular lead will be directly proportional to the number of isoflow lines which the wave front crosses. It is these streamlines which the model developed by McFee and associates[5] demonstrates. They may also be demonstrated in the Teledeltos paper models. After the model has served its other purposes a thin border of silver ink is drawn around the entire periphery, and the electrodes on the extremities are cut off. All of the conducting border to one side of the two extremities involved (for example, right arm and left leg in the case of Lead II) is connected to one pole of an electrical source, and the remainder of the conducting border is connected to the other pole. The isopotential lines are mapped in the manner previously described. The resulting isopotential plot is approximately conjugate to the isopotential lines of the reciprocal field and therefore represents the isoflow function of the reciprocal field.

DISCUSSION

The models described in this paper constitute a relatively simple but effective means of demonstrating the application of the principle of reciprocity to electrocardiographic theory. Although lead vectors can be determined by primary energization of the cardiac doublet,[8,9] the comprehension of the process is simpler and the calculations are easier when reciprocal energization is employed. The concept of the reciprocal field is of particular value because lead vectors are a parameter of the field (gradient) and can be roughly estimated from an inspection of an isopotential plot of the field. Such information is not available in isopotential plots of primarily energized fields.

Although the models are not an exact duplication of the human body, they indicate accurately the manner in which an electric doublet contributes to the formation of an electrocardiographic lead. The laws of this relationship are depicted graphically by the Burger triangle and the triaxial reference system (Fig. 3) derived from the Burger triangle. For exactness in summating the effects of a great number of doublets it would probably be necessary to establish many Burger triangles throughout the cardiac region. However, we have limited our determinations to three fairly representative points in each model; point *A* for the

electromotive forces arising from the right ventricle, point *B* for the septum and point *C* for the left ventricle (Fig. 1).

The results of these model experiments shed considerable light on the "validity" of the Einthoven triangle. It is apparent that the human body is not a flat, electrically homogeneous, equilaterally triangular volume conductor with a relatively small heart at its center. Nevertheless, the possibility should be explored that the Einthoven triangle, as a frame of reference, may express the relationships between the electrical activity of the heart and the extremity leads rather well. Experiments involving the introduction of an artificial doublet into the esophagus[15] or right ventricle of the heart[16] appear to demonstrate surprisingly good correlation between the electrocardiographically and roentgenographically determined axes of the doublet. On the other hand, Wilson and associates,[17] by reciprocally energizing human subjects, determined triangular frames of reference that were decidedly nonequilateral. The Burger triangles of our models more nearly approximate those of Wilson's human subjects than they do the equilateral form. On this basis, generalized triaxial (Fig. 3) and hexaxial (Fig. 4) reference systems formed from Burger triangles and their medians are decidedly more accurate than the special forms derived from the equilateral triangle. It was somewhat surprising that the introduction of electrical inhomogeneities in the models did not produce a more remarkable distortion of their Burger triangles than occurred. The conclusion is suggested that electrical inhomogeneities of the human body may not have as profound an effect on the electrocardiogram as might be anticipated.

Application of the principles of reciprocity and superposition to unipolar extremity leads indicates that any special merit possessed by such leads probably derives from a favorable orientation of their lead vectors and not from their possible unipolarity. As indicated in Fig. 5, synthetic leads may be formed whose lead vectors have any desired orientation. Such leads with horizontally and vertically directed lead vectors should be useful in the registration of vectorcardiograms. Other synthetic leads,[18] because of a uniquely favorable orientation of their vectors, may prove to be a valuable supplement to the Einthoven and unipolar extremity leads. This idea gains some support from an inspection of the hexaxial reference system shown in Fig. 4 where it is seen that there is a relatively large angular separation (approximately 60 degrees) between the Lead I axis and the lead axes to either side of the Lead I axis. If the lead axes of the human body approximate those of Fig. 4, these large angular areas might profitably be "explored" with additional synthetic leads.

The models described in this communication have proved easier to construct and operate than electrolytic tank models. Freedom from polarization has been particularly advantageous. This feature permits the use of alternating current frequencies low enough that disturbing capacity-to-ground effects are obviated and phase shift has not been noted. Areas of electrical inhomogeneity are easier to produce and explore than in tank models. Because of the relative simplicity with which reciprocal fields and their parameters are demonstrated by these models, they have proved a valuable adjunct in the teaching of electrocardiographic theory.

SUMMARY

1. A method has been described for constructing relatively simple two-dimensional models of the human body which demonstrate the quantitative relationships between currents of cardiogenic origin and the various extremity leads of the electrocardiogram.

2. The relationship between lead vectors and the electrical fields produced by reciprocally energizing the various lead pathways has been demonstrated.

3. Sets of Einthoven lead vectors (Burger triangles) for three representative regions of the model heart under various conditions of electrical inhomogeneity of the model have been demonstrated.

4. The possibility of generalizing the triaxial and hexaxial reference systems has been discussed, and a method of "fitting" such generalized systems to particular sets of lead vector data has been described.

5. The theory and method of forming synthetic leads having any desired orientation of their lead vectors has been described. The possible advantages of such leads have been discussed.

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Clinical Reports

THE HEART IN HEMOCHROMATOSIS

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SHELDON,[29] in 1935, collected and reviewed 325 cases of hemochromatosis from the literature. He mentioned that there was an increased deposition of iron in the myofibrils of the myocardium, but as a rule, there was no corresponding fibrosis. No mention was made that congestive failure was of serious consequence in this condition. However, cases of hemochromatosis presenting cardiac involvement were subsequently reported.[3-9,14-16,18,20,25,31] Congestive heart failure was observed in approximately 5 per cent of all reported cases, although large iron deposits were present in the heart in every case. Because congestive failure due to hemochromatosis is relatively rare, this case is being reported. Other findings presented by this case are focal necrosis of the anterior lobe of the pituitary gland and the absence of the usual body fat depots. The mechanism for cardiac failure in this and other cases of hemochromatosis will be suggested.

CASE REPORT

J.B., a 36-year-old Mexican laborer, was first admitted to the hospital with the complaint of not having felt well for the past two to three months. He noticed increasing fatigability, and he had lost about 15 pounds. Two weeks before admission he developed marked polyuria and increased thirst but no increase in appetite. The family and personal history were otherwise noncontributory.

Physical Examination.—The patient was a tall, thin, bronzed Mexican man who was cooperative. He did not appear acutely ill, although he had obviously lost considerable weight. Positive findings were as follows: the point of maximum apical impulse was in the fifth intercostal space 10 cm. from the midsternal line. The sounds were of good quality, there were no murmurs and A_2 was equal to P_2. The rhythm was regular. The liver was felt four fingerbreadths below the right costal margin and was firm, not tender, but slightly nodular. The spleen was indefinitely palpable. The veins were dilated over the lower part of the abdomen. The skin had a dark brown hue especially over the exposed areas, slightly darker in the skin folds. There was some loss of tissue turgor. There was no edema.

Laboratory Findings.—The red blood cell count was 4.57 million; hemoglobin, 13.5 Gm., and white blood count, 5,500. The differential count showed 66 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, and 3 per cent baso-

From the Pathology Service and the Medical Service, Veterans Administration Hospital, Long Beach, Calif.

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phils. The erythrocyte sedimentation rate was 32 mm.* The Kahn test was negative. The urinalysis showed no abnormalities. The initial fasting blood glucose was 444 mg. per 100 c.c. The CO_2 combining power was 27.2 meq./L. The total cholesterol measured 206 per 100 c.c., the gamma globulin was 0.95 Gm. per 100 c.c. and the total protein was 7.5 Gm. of which 3.6 was albumin and 3.4 was globulin per 100 c.c. The prothrombin was over 70 per cent. After six days of diabetic management the fasting blood sugar was 229 mg. per 100 c.c. Bromsulphalein retention was 3 per cent in forty-five minutes. The cephalin flocculation was 2+ in twenty-four hours and 3+ in 48 hours. Thymol turbidity was 7.5 units. The total van den Bergh was 0.4 mg. per 100 c.c. of serum. The chest roentgenogram showed hilar calcification bilaterally, most marked on the right, but no other abnormality. A liver biopsy was performed and the tissue was specially stained for iron. The pathologist reported hemochromatosis and cirrhosis of the liver.

Hospital Course.—The patient was placed on a 2,200 calorie diet used for diabetic patients and gradually controlled on 30 units of NPH-insulin given before breakfast. The patient asked to be released before further contemplated procedures could be carried out. The final diagnosis at the time of discharge was idiopathic hemochromatosis with diabetes and cirrhosis of the liver.

The patient was followed in the diabetic outpatient department. It was difficult to control his diabetes and his blood sugar averaged about 300 mg. per 100 c.c. He received 40 units of NPH-insulin daily. Six weeks later the patient returned. He had a fasting blood sugar of 300 mg. per 100 c.c. and he also had 2+ sugar in his urine but no acetone. He had gained 10 pounds in the past week and had noticed swelling of his ankles but no shortness of breath. Blood pressure was 110/78 mm. Hg, and there was slight ankle edema. His erythrocyte sedimentation rate was 36 mm.; red blood cell count was 4.25 million, and the hemoglobin was 12.6 Gm. The total protein was 7.8 Gm. of which 3.4 Gm. was albumin and 4.4 Gm. globulin per 100 c c. of blood. The patient refused hospitalization at this time.

Second Admission.—Three days after his last visit the patient experienced a sudden paraumbilical, nonradiating pain for which he sought hospitalization. He was nauseated and vomited copious amounts of green material. He found relief by squatting. The pain became somewhat less severe six hours after its onset.

Physical examination.—The patient was acutely ill and very apprehensive. The blood pressure was 90/60 mm. Hg; the pulse was 120 and grossly irregular; the temperature was 100.4° F. The abdomen felt slightly tense, although there was a generalized rebound tenderness. The liver was palpated six fingerbreadths below the right costal margin and the spleen was palpated three fingerbreadths below the left costal margin. Bowel sounds were absent. There was slight pitting edema of the ankles, and there was no increase of pigmentation since the previous admission.

Hospital Course.—Supine and upright roentgenograms of the abdomen taken immediately after admission showed dilated small intestinal loops and some diffuse haziness consistent with paralytic ileus and ascites. The serum amylase was absent. The blood sugar was 250 mg. per 100 c.c., the blood chlorides reported as sodium chloride was 455 mg. per 100 c.c., the CO_2 combining power was 59 volumes per 100 c.c., and the urine showed 2+ sugar and a trace of acetone. Roentgenogram of the chest showed an increase in heart size as compared with the heart size at the previous admission and also pulmonary congestion (Fig. 1). The venous pressure was 140 mm. of water and the electrocardiogram showed many auricular premature beats (Fig. 2,A). The patient was treated with gastric intubation, insulin, intravenous glucose in saline, and antibiotics. Two days later the abdomen was soft, and the rebound tenderness disappeared. The blood urea nitrogen was 21.5 mg. per 100 c.c. The urine showed 4+ sugar, 2+ acetone, and 1+ albumin. The patient was completely digitalized with 1.6 mg. of digitoxin and maintained on 0.2 mg. of digitoxin daily. He lost 5 pounds in the twenty-four hours following digitalization. Three days following admission, the serum amylase was 58 units and the serum lipase was 0.5 unit. On the fourth day after admission, the bowel sounds had returned and the abdominal tenderness completely disappeared. A week following admission, the patient had improved considerably and was able to eat a soft diet. At that time a plain roentgenogram of the abdomen revealed a normal picture. There was still slight pitting edema of the ankles and on examination there was some

*Wintrobe method.

questionable shifting dullness in the abdomen not noticed on admission. The patient was given 2 c.c. of Thiomerin subcutaneously and he lost 6 pounds in twenty-four hours. Three weeks after admission, a gastrointestinal series was done. The stomach and duodenum appeared normal, but an enlarged, unusually dense liver shadow was seen. The day following roentgenogram procedure, the patient developed epigastric burning which increased in severity in spite of antacids and antispasmodics. Again he became nauseated and was unable to retain food. The blood pressure fell to 80/50 mm. Hg, moist râles were heard in the left base, and the cardiac rhythm became grossly irregular (Fig. 2,*B*). There was then definite shifting dullness in the abdomen, and the ankle edema increased. He was given Demerol Hydrochloride, intravenous glucose with Aureomycin Hydrochloride, and 25 Gm. of salt-free serum albumin. The urine showed a trace of sugar. The patient's condition rapidly deteriorated and just before death he was started on intravenous ACTH, 20 mg. per day. However, he quickly became cyanotic, developed Cheyne-Stokes respiration, and died suddenly one month after admission.

Necropsy was performed approximately six hours after death. The body was that of a Mexican man who was well developed, weighed approximately 140 pounds, and measured 70 inches in length. The skin pigmentation appeared to be increased. The degree of pigmentation was difficult to evaluate because of the patient's nationality.

There was approximately 1,000 c.c. of yellowish, clear fluid in each pleural space. The peritoneal cavity contained approximately 3,000 c.c. of yellowish, clear fluid.

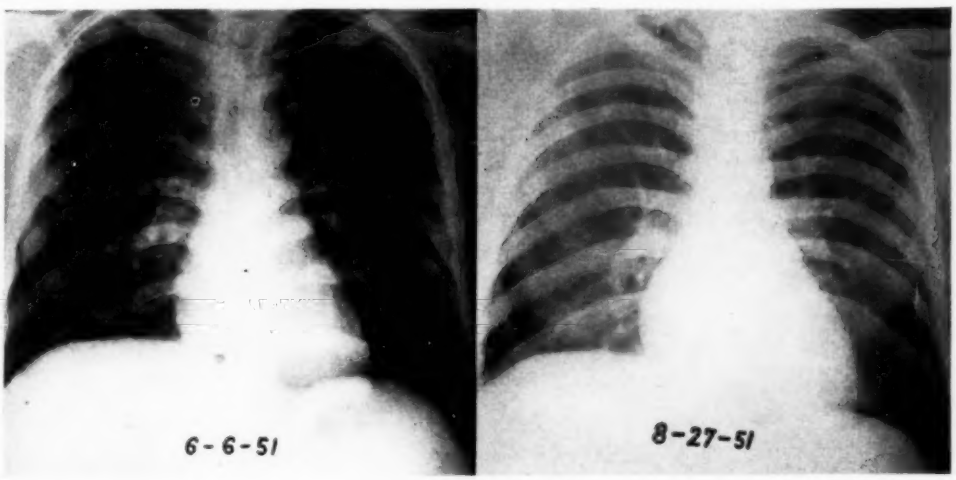


Fig. 1.—Posteroanterior view of the chest. The film of Aug. 27, 1951, shows definite diffuse cardiac enlargement with early pulmonary congestion.

The right lung weighed 900 grams and the left lung weighed 650 grams. They were firm and rubbery in consistency throughout, more so in the dependent portions. The lungs were markedly congested; grossly bloody fluid exuded from the cut sections. The tracheobronchial tree contained a moderate amount of frothy, clear fluid. The pericardial sac contained approximately 30 c.c. of clear, yellow fluid. The pericardial surfaces were smooth and glistening. The heart weighed 550 grams. The general configuration of the heart was that of a tear drop, and both ventricles were dilated. The walls of both ventricles were hypertrophied. The left ventricle varied in thickness from 20 mm. at the base to 10 mm. at the apex. The right ventricle measured from 3 to 6 mm. in width. The tricuspid valve was 14 cm., mitral valve 12 cm., aortic valve 7 cm., and pulmonic valve 8 cm. There were no abnormalities of the valves noted. The myocardium appeared yellowish-orange to brown in color throughout. The muscle was soft and flabby. There was no fibrosis evident in sectioning the myocardium. The myocardium showed an immediate Prussian blue reaction. The coronary ostia were open and the coronary arteries were patent throughout.

Atherosclerotic changes were not present in the coronary vessels. The aorta and major vessels were free of atherosclerosis with the exception of an occasional fine yellowish streak.

The liver weighed 2,400 grams. Its surface was finely granular except over the right anterior dome, the site of a previous liver biopsy, where there was some fibrotic thickening. The liver cut with difficulty and the cut surface appeared finely granular and orange to reddish-brown in color.

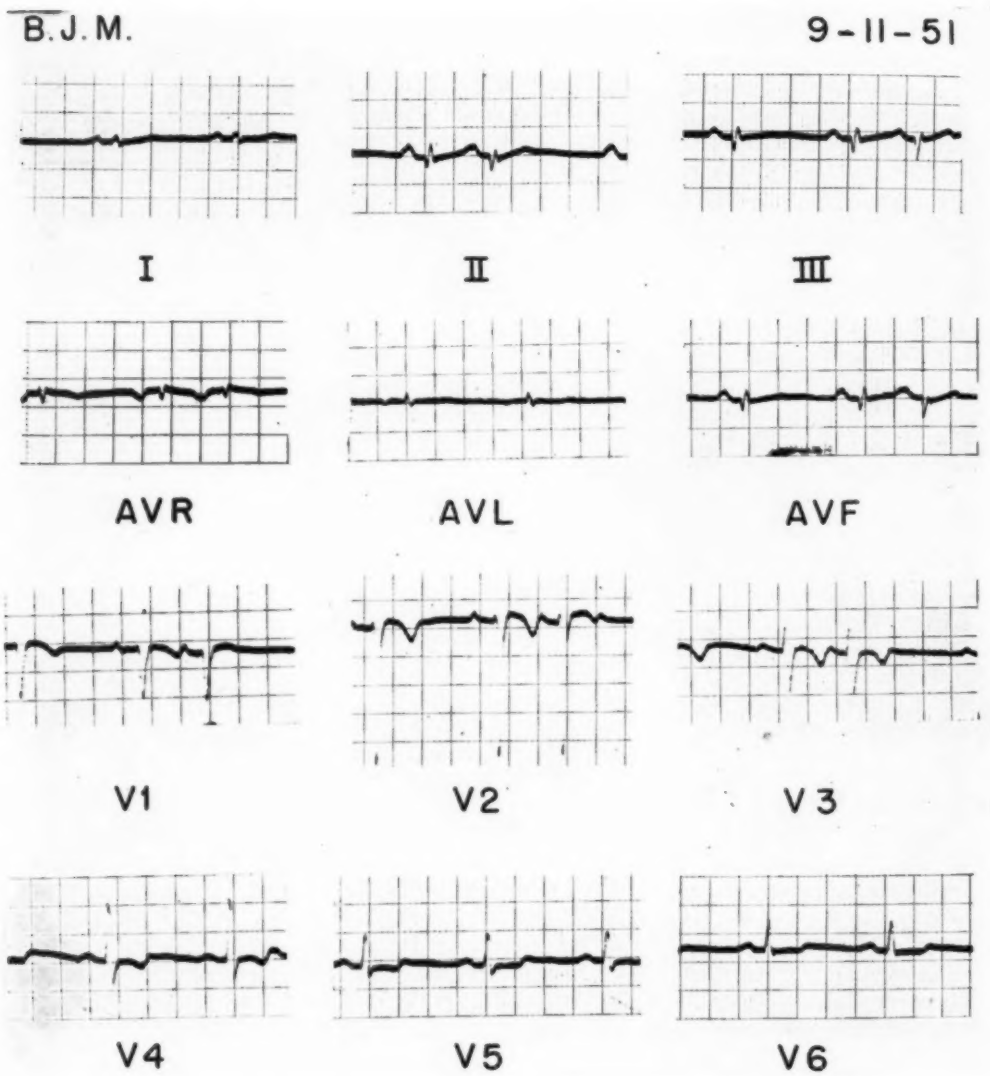


Fig. 2.—*A*, Many auricular premature contractions are present. In addition, there is S-T segment depression across the precordium plus T-wave inversion.

The Prussian blue reaction was promptly positive for hemosiderin. The spleen weighed 350 grams; its capsule was slightly thickened; the parenchyma cut with some difficulty and the densely fibrous pulp partially obscured the malpighian corpuscles. The pancreas weighed 150 grams; the parenchyma showed a dark brown pigmentation and increased fibrosis. The pancreatic vessels, ducts, and splenic vessels appeared normal.

The periesophageal and periaortic lymph nodes were prominent and on sectioning appeared dark brown. There was some diminution in the size of the testicles. There was almost complete absence of the usual fat depots in the subcutaneous, mesenteric, and retroperitoneal areas. The vessels of the mesentery were exceptionally prominent as the mesentery was transparent.

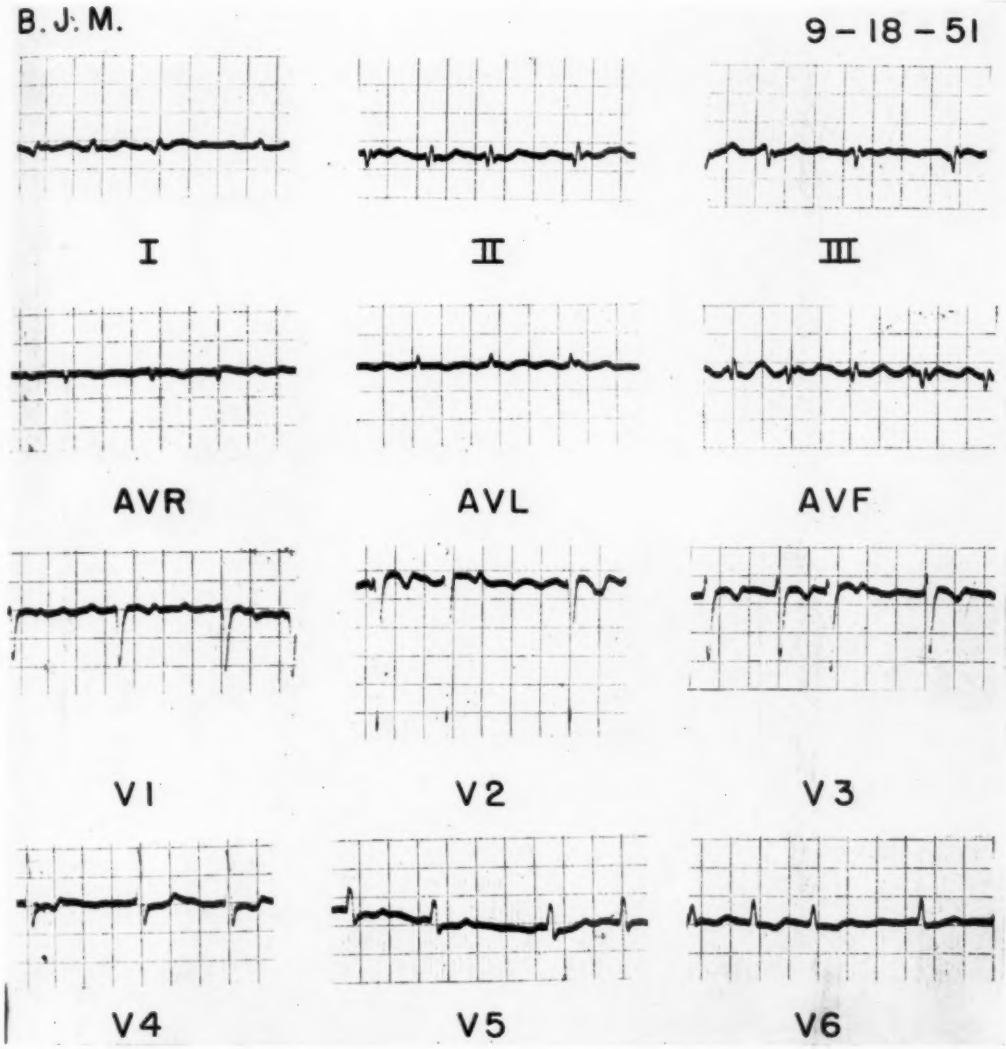


Fig. 2B. *B*, Auricular fibrillation flutter present now. (From Veterans Administration Hospital, Long Beach, Calif., Medical Photography Dept.)

Microscopic Findings.—

Lungs: The alveoli were distended with pinkish fluid. The alveolar capillaries were congested. Some areas of the interstitial tissue and the alveolar septa were markedly infiltrated with dark brown pigment granules. These stained positively with Prussian blue.

Heart: The pericardium was thickened and contained areas of round cell infiltration consisting mainly of plasma and mononuclear cells. The myocardial fibers were hypertrophied. The nuclei were increased in size and the ends were blunted and barrel shaped in appearance. Interstitial edema was marked as evidenced by wide separation of the myocardial fibers. The entire myocardium showed a diffuse pigmentation which seemed to be somewhat greater in the perivascular areas. The granules stained positively with Prussian blue. The interstitial tissues showed focal collections of mononuclear cells, some of which contained brown granules. The individual

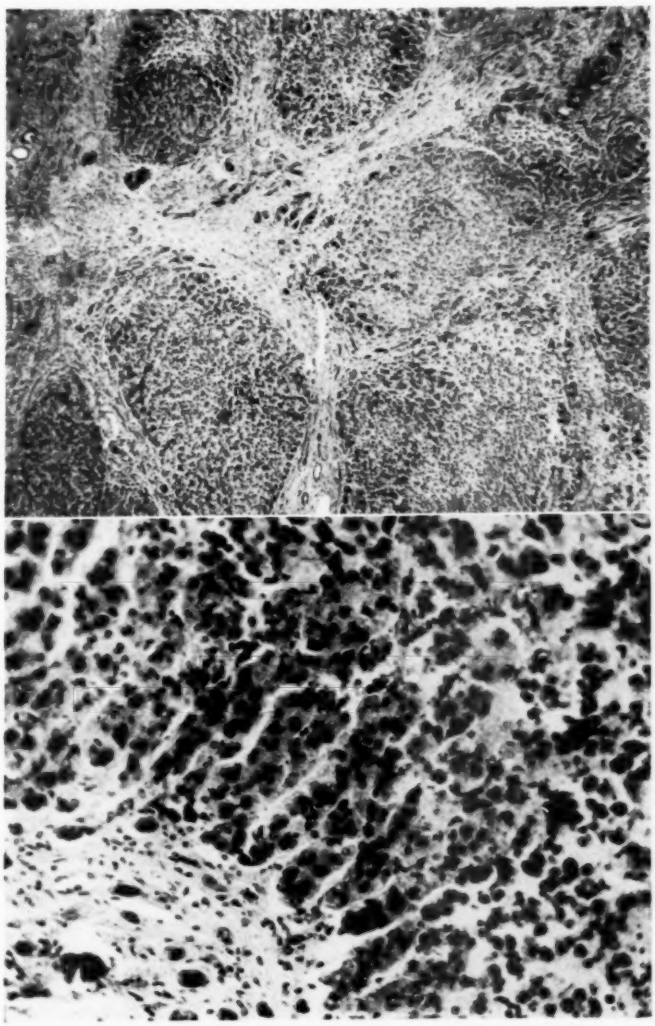
Fig. 3.—*A*, Heart showing vacuoles in myocardial fibers. Stains with sudan IV were positive for fat. Hematoxylin-eosin stain 60×.

B, Heart. Higher magnification of *A*. Hematoxylin-eosin stain 200×. (From Veterans Administration Hospital, Long Beach, Calif., Medical Photography Dept.)

myocardial fibers showed marked swelling and contained numerous small vacuoles in addition to the already-mentioned pigment. The vacuoles stained red with sudan IV, which was indicative of extensive fatty degeneration of the myocardium (Fig. 3, *A* and *B*).

Spleen: The venous sinusoids were markedly congested with red blood cells and mononuclear cells, the latter containing brownish pigment. The lymph follicles were normal.

Liver: The normal architecture was completely unrecognizable. Central veins were not readily identified. The parenchyma varied in appearance; in some areas it was completely replaced by fibrosis, in others the hepatic cellular cords appeared normal, and in still others the cells appeared in various stages of degeneration. Bile duct proliferation and fibrosis were prominent in the periportal areas. A cellular infiltration consisting chiefly of plasma cells, histiocytes, and lymphocytes was seen in the periportal areas as well as in areas of degenerating liver cords. He-



C.

D.

Fig. 3.—*C*, Liver showing cirrhosis with pseudolobulation, bile duct proliferation, and collections of pigment. Hematoxylin-eosin stain 60×.

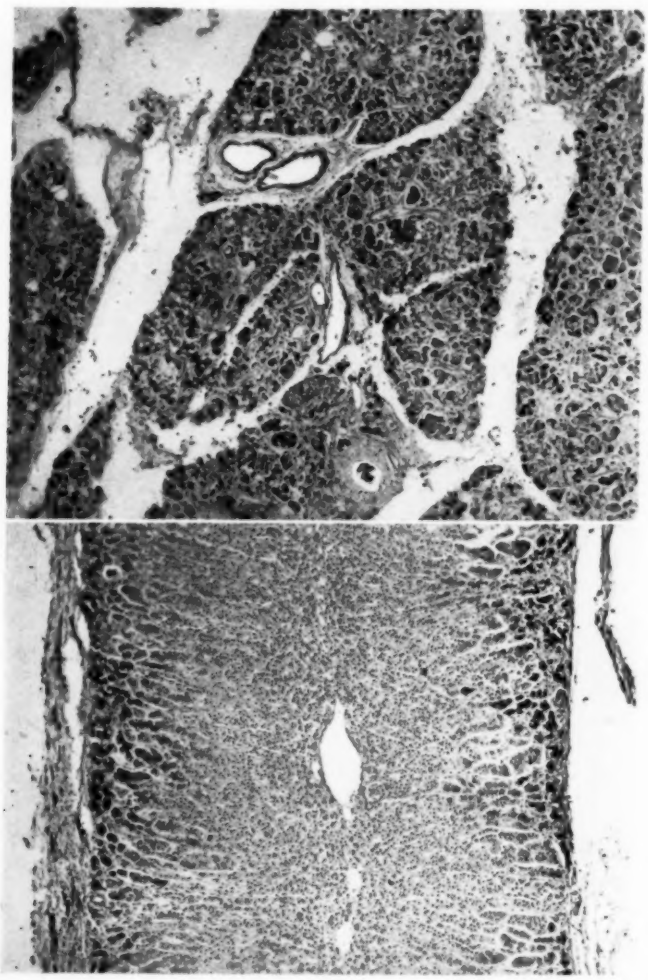
***D*, Liver showing collections of pigment (hemosiderin and hemofuscin) within hepatic cells and Kupffer cells. Note necrosis in lower left corner. Prussian blue stain 200×. (From the Veterans Administration Hospital, Long Beach, Calif., Medical Photography Dept.)**

patic cells, the cells lining the biliary ducts, and the Kupffer cells contained large quantities of brown granules. These stained positively with Prussian blue (Fig. 3, *C* and *D*).

Pancreas: The normal architecture was almost completely lost due to replacement by fibrous tissue. The cells lining the acini were completely destroyed and only a smudgy, eosinophilic

mass containing clumps of brownish pigment granules remained. The nuclei for the most part were either disintegrating or were completely destroyed. No islets of Langerhans were identifiable. The duct system showed the presence of inspissated secretions (Fig. 4, *A*). The arterioles revealed no significant change. Throughout the pancreatic tissue an occasional aggregate of mononuclear cells was seen. The Prussian blue stain again was strongly positive.

Adrenals: The normal architecture was preserved and there was brownish pigment seen predominantly in the zona glomerulosa and occasionally extended into the zona fasciculata (Fig. 4, *B*).



A.

B.

Fig. 4.—*A*, Pancreas showing diffuse interacinar fibrosis with secondary atrophy of the acini. Darker granules represent pigment deposition. Prussian blue stain 60×.

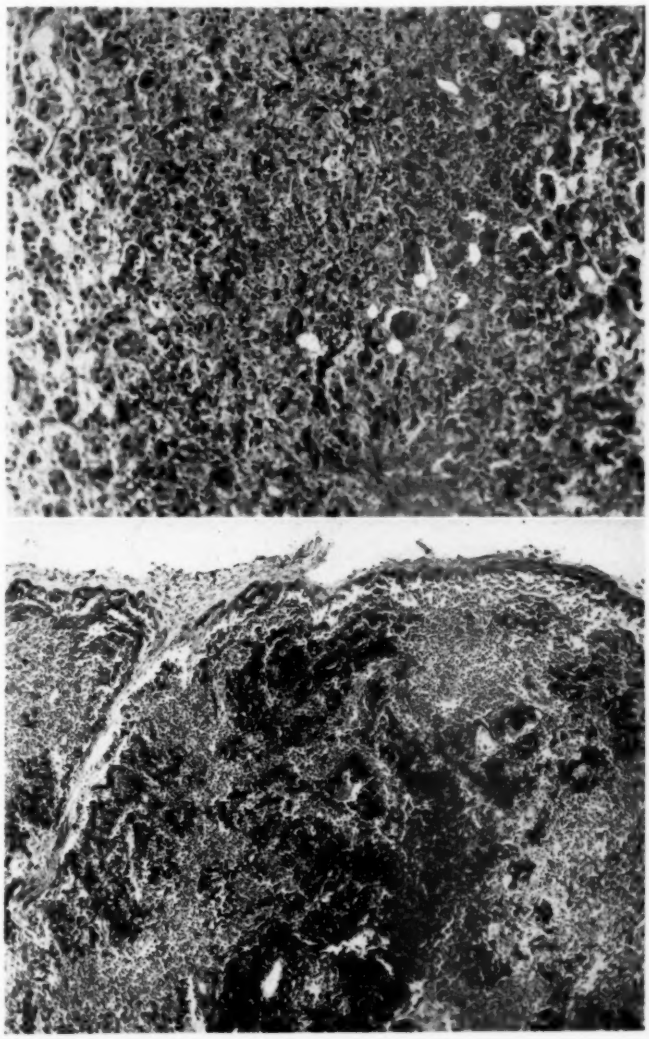
***B*, Adrenal showing prominent deposition of pigment in zona glomerulosa and outer layer of zona fasciculata. Note lack of other significant pathology. Prussian blue stain 60×. (From Veterans Administration Hospital, Long Beach, Calif., Medical Photography Dept.)**

Testes: The basement membrane was thickened and there was a diminution in spermatogenesis representing a Grade II testicular atrophy.

Pituitary: Numerous areas of focal necrosis of the parenchymal cells were noted throughout the anterior lobe. The reticulum was intact. The necrotic cells were replaced by homogeneous acidophilic substance and infiltration of numerous polymorphonuclear leukocytes and mononuclear cells. Throughout the gland there was considerable quantity of brown pigment (Fig. 4, *C*).

Lymph nodes: The abdominal nodes showed varying degrees of reticular hyperplasia and infiltration with brownish pigment. The pigment was chiefly seen in the littoral cells and in the free histiocytes. An occasional giant cell containing pigment was present. The pigment again stained positively with the Prussian blue stain (Fig. 4, *D*).

Skin: (Anterior abdominal wall.) The basal layer contained brownish pigment which was shown to be melanin.



C.

D.

Fig. 4.—*C*, Pituitary showing extensive necrosis in central portion of section with inflammatory cell infiltrates. Hematoxylin-eosin stain 100×.

D, Abdominal lymph node showing massive accumulation of pigment throughout. (From Veterans Administration Hospital, Long Beach, Calif., Medical Photography Dept.)

DISCUSSION

The following findings relating to the heart are considered characteristic of hemochromatosis. Clinically, right and left heart failure occurred in male patients under 40 years of age with no evidence of intrinsic heart disease such as arterio-

sclerosis, hypertension, or rheumatic fever. In addition to failure, arrhythmias and ST-T segment changes in the electrocardiogram are common. Auriculoventricular block, paroxysmal auricular tachycardia, auricular fibrillation, auricular flutter, and numerous ventricular extrasystoles have been described.[18,25,32] Radiographically, the heart is diffusely enlarged and similar in appearance to the heart of beriberi or active rheumatic carditis.[32] Pathologically, all chambers are diffusely enlarged due to hypertrophy and dilatation, and the myocardium is flabby and shows brown pigmentation.

The French authors,[9,24] in the twenty cases they have reported under the heading of *Endocrine hepato-cardiac syndrome*, ascribe the congestive failure to the involvement of the endocrine system due to hemochromatosis, rather than to the intrinsic involvement of the heart due to abnormal pigment. In support, they cited that the cardiac findings were much less striking than the endocrine involvement, having found only slight to moderate pigmentation of the myocardium and the heart soft and dilated. However, the endocrine findings that they mentioned, namely infantilism, testicular atrophy, loss of hair, palmar erythema, etc., are seen commonly in all types of cirrhosis of the liver including that due to hemochromatosis.

Other authors tried to correlate the congestive failure with the extent of the microscopic anatomic findings. Blummer and Nesbitt,[4] Horns,[18] Tucker and associates[32] and Petit[25] stated that the myocardium is characterized by various degrees of infiltration with pigment, degeneration, and replacement fibrosis of the myofibrils. Lyon[22] in one case found more hemosiderin in the heart than in the other organs.

The exact nature of the damage due to the iron in hemosiderin is still unknown. There is apparently no correlation between the amount of fibrosis and the extent of hemosiderin deposits in the various organs. Many authors feel that there are other factors, many of which are still unknown, besides iron in hemosiderin which must be present in order that fibrosis result from an increase in iron deposition in various tissues.[13,27] For example, in cases of pernicious anemia and malaria there is an increased iron storage in the liver, yet there is no fibrosis seen.

In the case reported here the classical findings of increased iron deposition and resulting fibrosis were seen in the liver, pancreas, and spleen. Other organs, kidney, adrenals, lymphoid tissue, thyroid, and pituitary, showed only pigment changes. The heart, however, revealed something quite different and interesting. In addition to the large amount of iron seen in the myofibrils and occasional interstitial cells, there was also marked interstitial edema and fatty degeneration of the myofibrils, but there was no evidence of interstitial or replacement fibrosis of the myocardium. The iron content of the myocardium in this case was 65 mg. per 100 Gm. of embalmed tissue.* Microscopic examination of this and two other cases and comparison with published photomicrographs demonstrated in this case the usual amount of iron seen in the heart in hemochromatosis. Fatty degeneration of the myocardium as seen in Fig. 3, *A* and *B*, was the most striking

*The amount of iron in a normal heart was 2 mg. per 100 Gm., while in a case of secondary hemosiderosis the iron content was 25 mg. per 100 Gm. of embalmed tissue.

pathologic finding. These findings were mentioned by others.[3,20,25] Tucker and associates[32] reported vacuolization of the myofibrils but special fat stains were not done.

Anderson[2] defined fatty degeneration as the appearance of visible fat in parenchymatous cells of such organs as liver, kidney, and heart. These changes indicate severe injury to the cells and may alter the physiologic function of the organ, but may be reversible. They are seen commonly in anemias or anoxemias, phosphorous poisoning, chloroform, benzene, and carbon tetrachloride poisoning, and in severe infections. The fat is not only invisible fat turned visible, but there is also additional fat from other sources in the body (Dibble and associates).[10,11] Hall,[17] in discussing these fatty changes in the heart, states that they may be the cause of severe cardiac failure.

We feel that the extreme degree of fatty degeneration of the heart seen in our case caused congestive failure and death. It is not unreasonable to suppose that the extreme fatty degeneration is a phase in the development of the eventual fibrosis seen in the myocardium in response to the toxic action of the high serum iron and the increased iron storage. In this case the changes seen in the heart may represent an early pathologic phase in the development of myocardial fibrosis. Further observations with special attention to the demonstration of fat in the myocardium may help to clarify some of these problems.

Two further unexplained findings heretofore unreported were observed: (1) acute focal necrosis of portions of the anterior lobe of the pituitary and (2) absence of body storage fat. Previously, only pigment changes of the anterior lobe of the pituitary had been reported by Sheldon.[29] One may speculate that if this patient had lived he might have developed hypopituitarism, thus simulating a Sheehan's syndrome.[19,28] Review of the literature with respect to fat metabolism in Laennec's cirrhosis, diabetes mellitus, hemochromatosis, and hypopituitarism does not suggest any mechanisms to explain the absence of body storage fat in this case.[12,21,33]

SUMMARY

A case of hemochromatosis with death due to heart failure has been presented. The literature has been reviewed with respect to the pathophysiology of congestive heart failure due to hemochromatosis. The possibility of fatty degeneration of the heart as a precursor of myocardial fibrosis was discussed. In addition, the findings of focal necrosis of the anterior pituitary and lack of body storage fat are reported.

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SYMMETRICAL PERIPHERAL GANGRENE COMPLICATING PULMONARY EMBOLISM

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BILATERAL symmetrical gangrene has been recognized as occasionally occurring in varied clinical conditions which result in severe circulatory collapse. It is well known in cases of circulatory failure caused by cholera.[1] Abramson[2] recorded it in a review of ball thrombi of the heart, in which condition it has been more recently documented by Evans[3] and by Evans and Benson.[4] Perry and Davie[5] observed bilateral symmetrical gangrene of the lower limbs in a case of hypertensive heart disease terminating in congestive failure. Chatterjee[6] noted incipient peripheral symmetrical gangrene during the course of lobar pneumonia. It was reported as a complication of paroxysmal ventricular tachycardia by Abrahams,[7] and following myocardial infarction by Swan and Henderson.[8] Most authors have agreed with Fishberg[9] that the responsible mechanism in such cases is extreme peripheral vasoconstriction.

We have recently observed a patient with bilateral symmetrical gangrene of the extremities and nose which followed massive pulmonary embolism. As this is apparently a unique case, we feel that it justifies the following report.

CASE REPORT

C.R.H., a 51-year-old white man, was admitted to the State Hospital with symptoms of a depressive psychosis, after being confined to bed for three weeks. He had known hypertension for ten years, and had sustained a posterior myocardial infarction six years previously. For three years he had noted coldness of the extremities, and intermittent claudication.

On examination, he was in no acute distress. The blood pressure was 190/118 mm. Hg; the fundi showed moderate arterial sclerosis. The heart was enlarged to the left, with a regular rhythm at a rate of 90 per minute. There was a presystolic gallop rhythm at the apex, and the second aortic sound was accentuated. The feet were cool to touch, and the pulsations of the arteries at the ankles were diminished.

Routine laboratory studies, including blood count, urinalysis, nonprotein nitrogen, and serology were within normal limits. The electrocardiogram showed evidence of left ventricular hypertrophy, and residua of the old posterior myocardial infarction.

On the sixth day after admission there occurred a pulmonary embolus to the right lower lobe, which was manifested by severe right chest pain followed by hemoptysis. Examination revealed dullness at the right lung base, over which area the breath sounds were diminished. There was evidence of phlebothrombosis in the right calf, with local tenderness and a positive Homans' sign.

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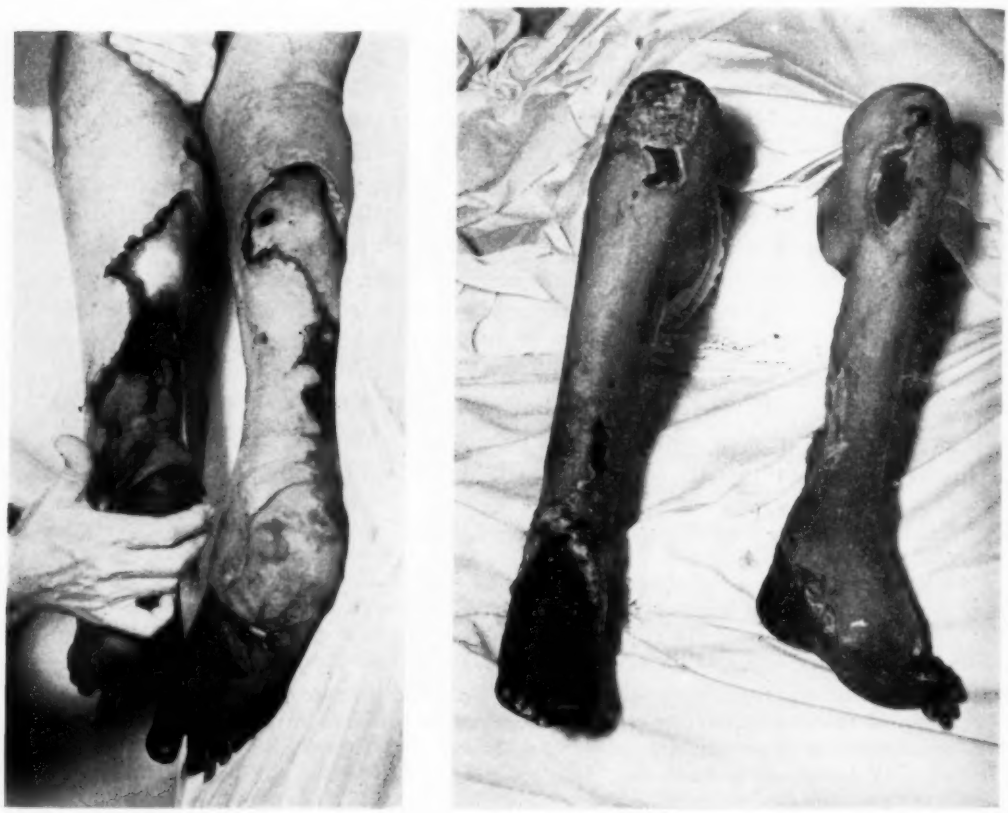
The presence of pulmonary infarction involving the right lower lobe was confirmed by a chest roentgenogram. The following day the patient had a similar acute episode, considered to be another embolus to the right base. Blood pressure continued at previous levels, and general condition remained good. He was given intravenous papaverine and aminophylline, and placed on strict bed rest. Anticoagulants were administered, consisting first of Depo-Heparin Sodium and later Paritol-C, to maintain the coagulation time at about thirty minutes.

On the tenth hospital day the patient developed acute, excruciating pain in the left chest, and went into a state of shock. There was marked cyanosis of the ears, nose, lips, hands, and feet. The blood pressure fell to 90/60 mm. Hg, with a thready pulse regular at 140 per minute. Emergency therapy was given, consisting of oxygen, morphine sulfate, papaverine, and intravenous fluids. After about four hours the blood pressure rose to 140/90 mm. Hg, and the patient became responsive. However, the marked cyanosis continued. Rare premature contractions were heard, and quinidine sulfate 0.2 Gm. every six hours was given orally.



A. *B.*

Fig. 1.—*A*, Posterior view of the feet and legs three weeks after the embolism. *B*, Anterior view at six weeks.

That night the patient expectorated bloody sputum, and a friction rub was heard at the left lung base. There was dullness over the left lower lobe, and breath sounds in that area were diminished. Bilateral lumbar sympathetic blocks were done daily for the next three days with no improvement. The cold, cyanotic areas in the toes extended proximally to involve the distal portions of the feet. There was a spotty, symmetrical distribution of cyanosis over the skin of the legs and lateral aspects of the thighs. However, the pulsations of the dorsalis pedis and posterior tibial arteries were felt as before. The nose and the nail beds of the fingers remained cyanotic, and large areas of bluish discoloration were noted over the lateral aspects of both upper arms.

The patient was then given continuous caudal anesthesia for the next week. Various peripheral vasodilators were administered with careful observation to prevent undue lowering of the blood pressure. These included intravenous papaverine, subcutaneous Bistrium Bromide, oral Priscoline, and oral niacin. The anticoagulants were continued, and he was kept in an oxygen tent. Penicillin was given in doses of 100,000 units each three hours, and dihydrostreptomycin 0.5 Gm. each six hours.

Six days after the last pulmonary embolus there appeared transient atrial fibrillation, with an apical rate of 125 per minute. This was converted to sinus rhythm within twenty-four hours with Cedilanid 2.0 mg. administered intravenously in divided doses, and the arrhythmia did not recur. Digitalization was subsequently maintained with Gitaligin 0.5 mg. daily. Serial electrocardiograms taken at intervals of one to three days showed no evidence of new myocardial infarction. On the day of the embolism there was a transient depression of S-T segments in leads from the anterolateral surface of the heart. The white count rose to 25,300, of which 90 per cent were polymorphonuclear cells showing a left shift. The platelets numbered 175,000, within normal limits for this laboratory. Total serum proteins were 6.8 Gm. per cent, with albumin 4.0, and globulin 2.8. Cooling of the serum did not result in precipitation of serum proteins, and cold agglutinins did not appear. There was no increased tendency for the blood to gel following collection.

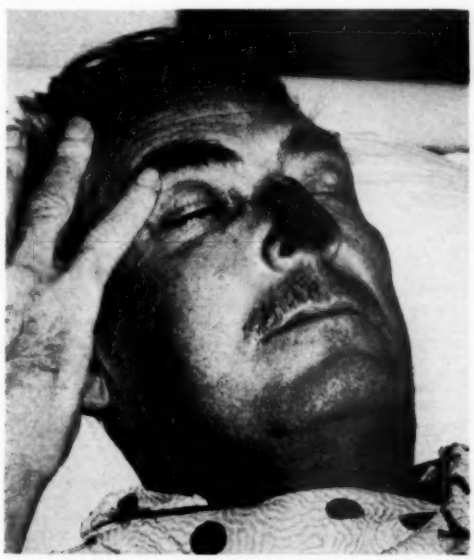


Fig. 2.—The gangrene of the nose three weeks after the pulmonary embolism.

The cyanosis of the ears and lips cleared in one week, as well as in the fingers except for two digits. There gradually appeared incipient and then frank gangrene of the distal portions of the second and third digits of the left hand, the tip of the nose, lateral aspects of the upper arms and thighs, the knees, spotty areas over the legs, and the feet. The gangrene in the peripheral portions of the lower extremities advanced proximally, and the pulsations of the arteries in the ankles disappeared. Fig. 1,*A*, shows a posterior view of the legs and feet three weeks after the embolism, and Fig. 1,*B*, shows an anterior view at six weeks. The gangrene of the nose at three weeks is shown in Fig. 2.

A pleural effusion developed on the left, and repeated thoracenteses were productive of 1,400 c.c., 1,300 c.c., and 450 c.c. of serosanguinous fluid having the characteristics of an exudate. A long course of supportive therapy was necessary, with blood transfusions given to correct a toxic anemia. The gangrenous areas in the lower extremities gradually became demarcated at the midleg level, but there was considerable tissue destruction over the right patella. The terminal

portion of the nose sloughed. The distal phalanges of the second and third fingers on the left likewise became gangrenous and demarcated (Fig. 3). There was only superficial destruction of the large involved areas on the lateral aspects of the thighs and arms, and these sloughed to leave healthy underlying tissue.

Reparative surgery was begun two months after the embolism, and consisted of amputation of the left leg at the midtibia, and an amputation above the knee on the right. The gangrenous distal portions of the fingers were then amputated. Skin grafts from the abdomen and left thigh were applied to the stumps of the lower extremities, and good healing was achieved. The patient was discharged six months after the admission, in fair general condition. He had no symptoms of mental depression at that time.

Microscopic sections of the amputated extremities showed multiple organizing thrombi of the arteries. The luminal diameter of the arteries was considerably diminished. There was marked variation in the thickness of the arterial walls, which showed extensive calcification.

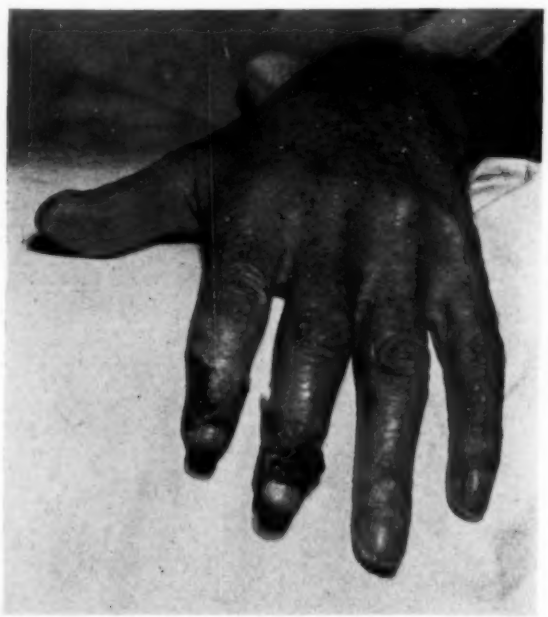


Fig. 3.—The appearance of the left hand at six weeks, showing the demarcated gangrenous extremities of the second and third digits.

DISCUSSION

Our patient had symptoms of peripheral vascular disease prior to the episodes of pulmonary embolism. The clinical impression of antecedent sclerotic disease of the peripheral arteries was confirmed by the microscopic sections of the amputated limbs. Pre-existing vascular pathology was likewise reported by Swann and Henderson[8] in a patient with peripheral gangrene following myocardial infarction, but their patient had Raynaud's disease.

The patient's third pulmonary embolus in four days was followed by marked circulatory collapse, after the first two had been well tolerated. The generalized cyanosis remained severe, despite improvement in the shocklike state in several hours. It is believed that a severe peripheral vasoconstriction of the arterioles developed as a reflex to a marked fall in cardiac output. This, superimposed

upon the pre-existing vascular disease, was a major factor in the severe cyanosis, which progressed to gangrene despite intensive therapy. Poor oxygenation of the blood in the lungs due to extensive pulmonary involvement was also contributory. During the early stages the major arterial pathways remained open. However, there gradually developed proximal advancement of the thrombosis in the lower extremities, and the arterial pulsations in the ankles disappeared.

The possibility of multiple small peripheral emboli appears unlikely in view of the initial generalized arteriolar involvement, and the subsequent course. There was no apparent source for such emboli, as there was no evidence of myocardial infarction or of subacute bacterial endocarditis. Transient atrial fibrillation appeared six days after the onset, but by that time the clinical picture was well established. The atrial fibrillation was considered significant in that it tended to augment the circulatory embarrassment. Abramson[1] believed that symmetrical peripheral gangrene in ball thrombi could be due to peripheral arterial emboli. However, Fishberg[9] suggested severe peripheral vasoconstriction in such cases as the causative factor. He considered intense cyanosis progressing to gangrene as a major point in the clinical diagnosis of occlusion of the mitral orifice, although occasionally caused by a tight mitral stenosis. None of the sections of thrombi in our case contained slitlike spaces of the type described in embolization with material from atheromas.[10]

Unusual conditions of intravascular clotting such as cryoglobulinemia[11] and essential thrombophilia[12] were ruled out by the laboratory studies. The effects of anticoagulant therapy, sympathetic nerve blocks, and peripheral vasodilators failed to prevent the loss of tissue and limbs. However, the treatment may have limited the advancement of the process, and thus aided in the survival of the patient.

SUMMARY

A unique case of symmetrical peripheral gangrene following pulmonary embolism is reported. Pre-existing peripheral vascular disease of the sclerotic type was present. Excessive peripheral vasoconstriction secondary to circulatory collapse is considered the principal factor, although poor oxygenation due to impaired pulmonary function contributed. The patient survived, but sustained extensive loss of tissue.

Seven months after discharge, the patient expired suddenly in another city. Post-mortem examination was not done.

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PATENT DUCTUS ARTERIOSUS AND CONGENITAL MITRAL STENOSIS

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THE association of patent ductus arteriosus and mitral stenosis is extremely rare. Donnally was able to collect only twelve cases of proven congenital mitral stenosis and some with a patent ductus arteriosus.[1] Recently, Douglas and associates[2] described a case of patent ductus arteriosus with a veno-arterial shunt with obstructive pulmonary vascular lesions. Swan and associates[3] reported on a case of congenital mitral stenosis with patent ductus arteriosus and coarctation of the aorta.

In the present case the association of patent ductus arteriosus and mitral stenosis afforded a unique opportunity for study of the distribution of cyanosis in patent ductus with a veno-arterial shunt and also of the angiocardiographic pattern. The changes observed during the operation will, perhaps, be of help regarding the advisability of operation in such cases.

CASE REPORT

This patient, a white infant girl, was 18 months old when first examined by us. The only child of healthy parents, she was born after a normal pregnancy. Since birth, a heart murmur was detected and she was eventually brought to our clinic due to dyspnea and fatigue. The past history revealed two attacks of bronchopneumonia.

She was an undernourished baby, with slight cyanosis of the toes. This localized cyanosis (Grade 2) was not permanent and sometimes disappeared completely. The femoral arteries were normally palpable. There was no clubbing of the fingers. The pulse rate was 108; the respiration rate, 60. The heart rate was regular. P_2 was markedly accentuated (Grade 4) and split. There was a distinctly heard diastolic murmur over all the precordium, maximum at the apex, with all the characteristics of a rumble (Fig. 1). The liver was palpable three fingerbreaths below the costal margin at the midclavicular line. The lungs were clear to percussion and the breath sounds were normal.

The roentgenogram (Fig. 2) showed an enlarged and normally placed heart with a small vascular pedicle. The cardiothoracic ratio was 0.66. The shadow of the left bronchus could be seen upwardly displaced, and the left auricle could be visualized within the cardiac shadow as a central area of increased density. The lungs were congested and the vascular markings increased. The left oblique view showed a posterior bulge of the cardiac shadow.

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The Electrocardiogram (Fig. 3) revealed a regular sinus rhythm with right axis deviation (+ 150 degrees). The P waves were notched in Lead I, tall and pointed in Lead II, diphasic (+−) in Leads V_{2R}, V_E, V_1, up to V_3. The QRS complex was formed essentially by an enlarged R wave in V_{2R}, V_E and V_1 and by a small R followed by a deep S wave in V_6. In conclusion, the electrocardiogram showed hypertrophy of the right ventricle and left auricle.

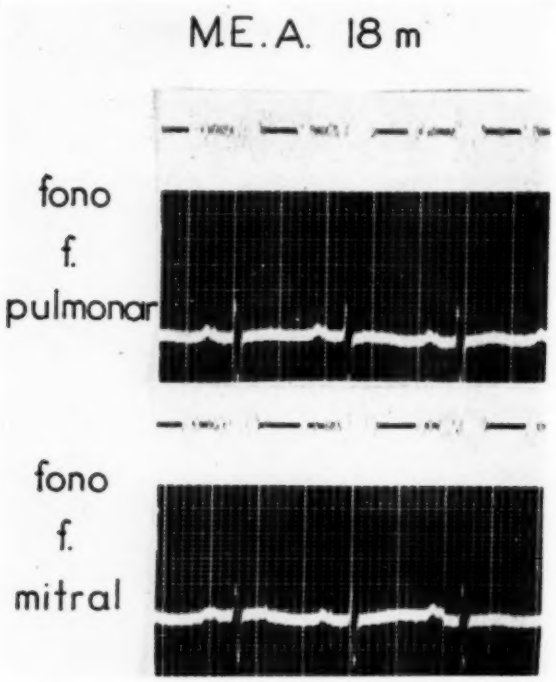


Fig. 1.—Phonocardiogram at the second left intercostal space (*fono f. pulmonar*) and at the apex (*fono f. mitral*).

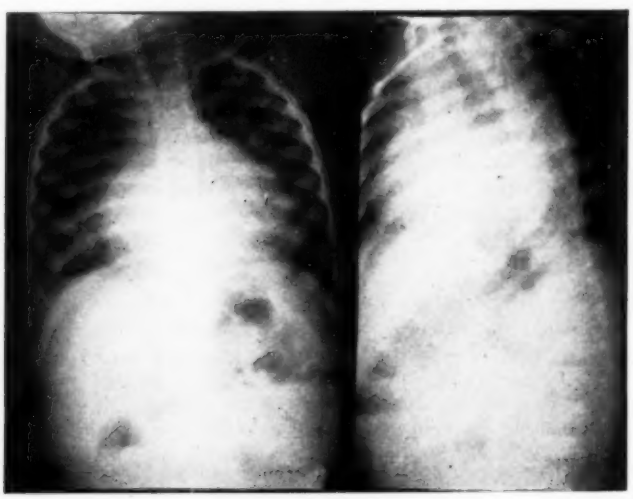


Fig. 2.—Teleröntgenograms in the posterioanterior view and in the left oblique view.

TABLE I.

PRESSURE*	OXYGEN SATURATION†
R. Auricle Syst. 15 mm. Hg	65
R. Ventricle Syst. 90	69
Aorta (descending) 108/68	80

*Due to AC interference during the recording, these numbers are only approximate.
†The oxygen saturation was obtained by oximetry.

The blood count was within normal limits.

The Catheterization of the heart was made through the saphenous route and we were able to catheterize the ductus through the pulmonary artery.

We were unable to obtain blood samples and pressures from the pulmonary artery due to clotting in the catheter.

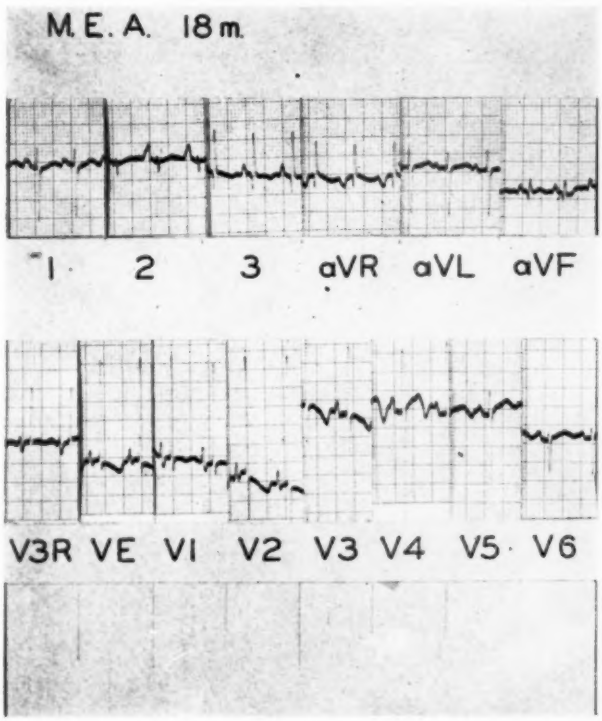


Fig. 3.—The electrocardiogram.

The Angiocardiogram was made in the left oblique position. In the second plate, at the moment of visualization of the dextroangiocardiogram, with the right ventricle and pulmonary arteries full of contrast, the aorta was visualized in its descending portion (Fig. 4).

In the last 2 plates the left cavities and the ascending aorta remained full of the contrast medium. In none of these plates, however, was the descending aorta clearly visualized.

It was concluded that the premature opacification of the aorta was due to a venous-arterial shunt through a patent ductus arteriosus, and that the nonvisualization of the descending aorta

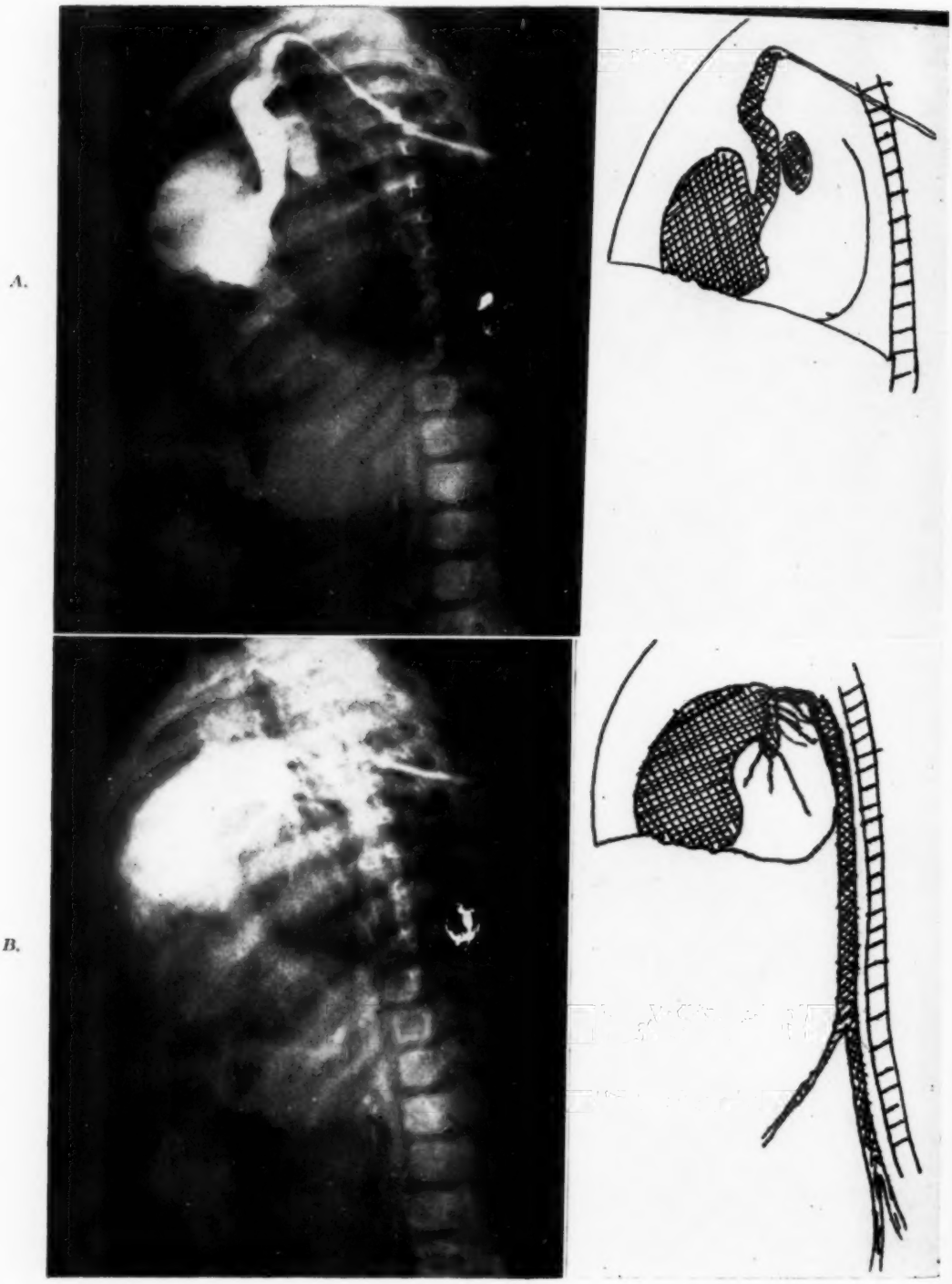
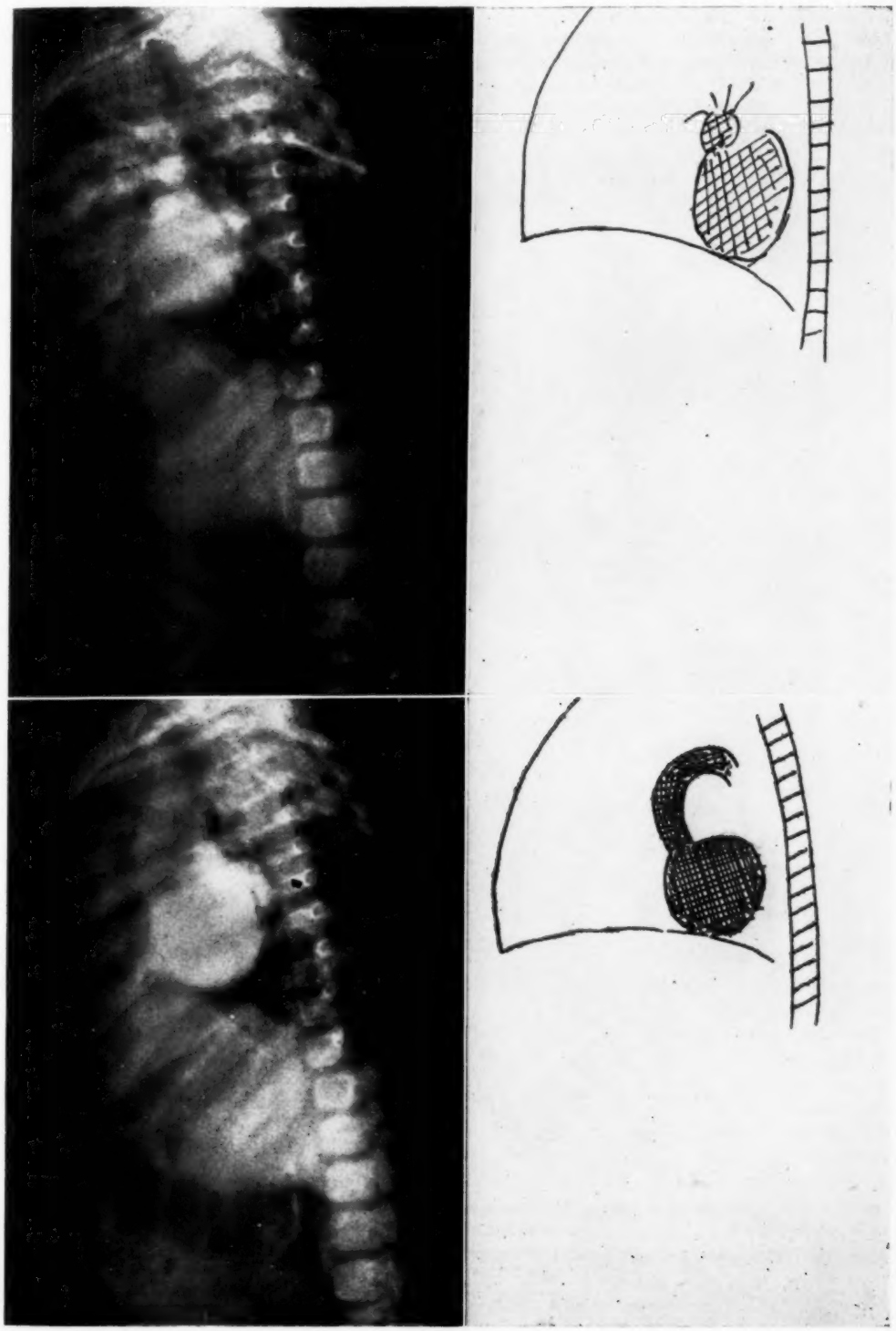


Fig. 4.—Angiocardiograms. *A*, One second after the end of the injection; *B*, two seconds. At two seconds the descending aorta is already opacified at the moment of the dextroangiocardiogram. *C*, At four seconds showing the beginning of the opacification of the left cavities; *D*, at six seconds the left auricle is definitely shown as well as the ascending aorta.



C.

D.

Fig. 4.—*C.* and *D.* (For legend see opposite page.)

during the levoangiocardiogram was due to the dilution of the contrast medium in the aorta by the blood flow coming from the pulmonary artery. The permanence of the opacification of the levoangiocardiogram during two seconds was confirmatory of the existence of mitral stenosis.

Fig. 5.

Fig. 6.

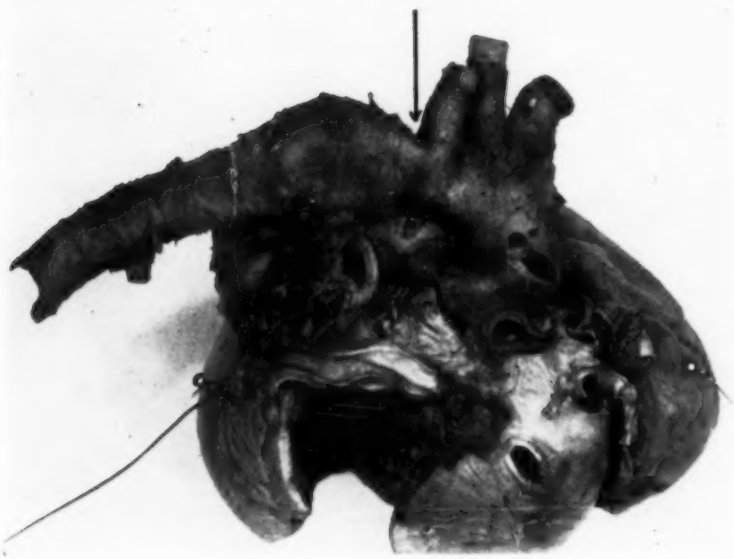


Fig. 5.—(*A*) Aorta; (*P*) Pulmonary artery; (*C.A.*) Ductus. The arrow marks the width of the ductus.

Fig. 6.—The aorta is shown and the arrow marks the site of external stricture distal to the left subclavian artery.

The baby did not improve or react to digitalization and her rapid downhill course forced us to resort to surgery. The preoperative diagnosis was: patent ductus arteriosus and mitral stenosis.

It was decided to explore first the ductus and during its temporary occlusion observe the reaction of the patient.

The operation was performed by Dr. José Hilário. The ductus was easily visualized, and it was large, the size of the aorta. The surgeon had the impression that the aorta was larger below than above the implantation of the ductus. The pulmonary artery was extremely large and pulsated intensely. During the temporary occlusion of the fistula, there was a marked elevation of the oximetric reading at the ear, the femoral pulse did not change, the bulging and the pulsation of the pulmonary artery diminished sharply and the surgeon observed that the thrill disappeared.

It was decided to go on with the occlusion and a triple ligature was made by the surgeon. Unfortunately, the child died two hours after the operation.

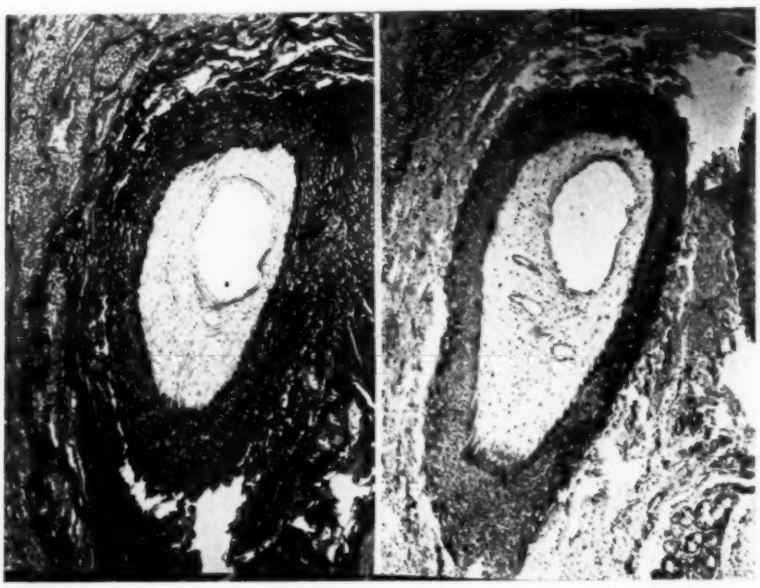
Autopsy.—The heart was enlarged, with a marked bulging of the pulmonary conus. Its right border was more horizontal and overlayed the diaphragm. The pulmonary artery had a normal origin, was dilated, measuring 20 mm., the main left branch measured 9 mm., and the main right branch, 7 mm. (Fig. 5).

Fig. 7.—The left auricular cavity is shown. (*M*) the mitral valve. (*A.E.*) The thickness of the left auricle.

The ascending and descending aorta had an average diameter of 12 mm. Just beyond the left subclavian artery, exactly at the point of origin of the ductus arteriosus there was a slight narrowing of the aorta and a small dilatation caudad (14 mm.). The internal lumen of the vessel, however, was widely patent, even at this point of external narrowing. All the aortic branches were normal (Fig. 6). The ductus arteriosus was patent, had a normal implantation and was extremely short, and its caliber was approximately the same as that of the aorta. However, the triple ligature prevented more exact measurements. The left auricle was extremely enlarged and with abnormally thick walls (3 mm.). The foramen ovale was closed. Pulmonary veins were normal. The mitral valve was greatly modified in shape, with thick valves completely fused together, and with undifferentiated cusps forming a funnellike orifice (Fig. 7). The left ventricle had a diminished capacity and its wall had a thickness of 10 mm. The right auricle and the venae cavae were normal, as were the right ventricle and the tricuspid valve. The average thickness of the myocardium of the R ventricle was 6 mm.

The pulmonary orifice was normal, and its internal diameter was 25 mm. The aortic orifice measured 22 mm. The anatomic diagnosis was patent ductus arteriosus and mitral stenosis.

Lungs.—The pleura was thickened in some places, due to a proliferation of connective tissue and vascular newformation. The parenchyma had a few areas of atelectasis but most of the alveoli were normally aerated. Surrounding a great number of bronchioles there were foci of neutrophilic infiltration. In the lumen of the majority of the alveoli, large cells were observed, with vacuolated cytoplasm and with a brown pigment (heart failure cells). In some of the larger arterial branches, in the vicinity of the hilum, the vascular lumen was reduced due to a thickness of the intima. In those places the intima was formed by very loose connective tissue, of the embryonic type with newly formed vessels (Fig. 8).



A. *B.*

Fig. 8.—*A*, Hematoxylin-eosin stain. Pulmonary arteriole showing a great reduction of the lumen of the vessel due to the thickening of the intima. The intima is formed by loose connective tissue with newlyformed capillaries. *B*, Weigert elastic tissue stain. Another pulmonary arteriole. The thickening of the wall is due to the connective tissue of the intima of the vessel. The internal elastic lamina is normal.

DISCUSSION

This is one of the rare cases of patent ductus arteriosus with venous-arterial shunt.

It is interesting to observe that the cyanosis that existed was of the toes, that is to say, the flow of venous blood through the ductus was directed only to the descending aorta. This, of course on purely theoretical grounds, should be expected, because the flow of blood coming from the left ventricle to the ascending aorta was normally oxygenated and it would be improbable that the flow coming from the ductus to the aorta would go backwards against the current. Therefore, any cyanosis that appears should be localized or predominant on the inferior part of the body. Another point of interest was the intermittence of the cyanosis, indicating, perhaps, the reversal of the flow.

In several articles[4,5] on cyanosis in patent ductus arteriosus (excepting those with coarctation of the aorta) no mention was found that it was localized at the inferior part of the body, which, we think, would be the normal expectation in such cases.

The so-called continuous murmur typical of a patent ductus was not found in this case. The murmur that existed was only diastolic and with the characteristics of a rumble of a mitral stenosis. As a matter of fact, we did not suspect the patency of the ductus until we made the angiocardiogram and catheterization. There are other cases reported of patent ductus without a typical murmur and in several this was attributed to the pulmonary hypertension, diminishing the gradient of pressure between the aorta and the pulmonary artery.

On the other hand, in a recent article,[6] a revision was made of the causes of diastolic murmurs at the apex in congenital heart lesions. Several of the cases reported were examples of patent ductus arteriosus, but none with an associated mitral lesion, and in all of them the author attributed the mitral murmur to a relative mitral stenosis. In this case we listened to the heart just after the closure of the thorax and the murmur persisted with the ductus ligated.

The data obtained from the electrocardiogram—the marked right ventricular hypertrophy—confirmed once more the dictum that signs of right axis deviation or right ventricular hypertrophy in a ductus, are indicative of a complicated ductus, associated with some other lesion.

Another point of interest was the data obtained from the angiocardiogram. If, in the average case of patent ductus arteriosus, the angiocardiogram is of limited value due to the arteriovenous shunt, when the shunt is veno-arterial, the angiocardiogram becomes a method of choice for confirmation of the diagnosis, because the aorta should be visualized twice and each time in a different portion of the vessel.

When the contrast is in the right side of the heart and the pulmonary artery is visualized, there should be, as in the reported case, a visualization of the descending aorta, distal to the implantation of the ductus arteriosus, and at the moment of the levocardiogram, there should be a second visualization of the aorta, but now, at the ascending portion of the vessel up to the ductus. After the ductus arteriosus, the contrast medium in the aorta will be diluted by the blood coming from the pulmonary artery. Depending on the amount of the shunt, this dilution may diminish the contrast visualization, or even abolish completely the visualization of the aorta beyond the ductus, as in the case herein reported.

A last point to be discussed is the indication for ligation of a ductus when there are associated lesions. All authors agree that the ligation is contraindicated when this anomaly is associated with other congenital cardiac defects for which the circulation through the ductus is a compensation.

The association that existed in our case, however, was not of the type to which we could attribute a compensatory action to the patency of the ductus. It could be acting as an escape valve for the pulmonary circulation. If this was the case its closure should lead to an increase of the pulmonary tension, leading eventually to pulmonary edema.

The diminution of the size and of the bulging of the pulmonary artery that was observed after the temporary occlusion of the ductus indicated that this was not the case and that the tension in the pulmonary artery diminished after the occlusion. At autopsy we searched carefully for signs of pulmonary edema, but none could be found.

To explain this abrupt diminution of the tension of the pulmonary artery, coincident with the closure of the ductus, we have to admit a hypothetical vasoconstrictive effect in the pulmonary arterioles. It seems fair to conclude that the pulmonary hypertension in this case was due, in part, to an increased pulmonary blood flow, and in part to the mitral stenosis. Furthermore, since the closure of the ductus would result in a marked reduction of pulmonary blood flow and pulmonary hypertension, operation could be indicated even under these circumstances.

SUMMARY

The clinical and pathologic findings of an 18-months-old girl with a patent ductus arteriosus and mitral stenosis are presented.

The distribution of cyanosis and the auscultatory data are analyzed. The angiocardiographic pattern of a patent ductus arteriosus with a venous-arterial shunt is described.

The mechanism of pulmonary hypertension and operation are discussed.

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DEFECT OF THE AORTIC SEPTUM

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IN 1950 one of us[1] reported a patient with a communication between the aorta and the pulmonary artery just above the valves, briefly reviewing the literature[2] and discussing the methods of diagnosis. The thought was expressed that the lesion is more common than has been believed. This has been borne out to some extent because since then a number of papers on the condition have appeared.

Gibson, Potts and Langewisch[3] reported four patients considered to have the anomaly. Each had been subjected to exploratory operation because of the possibility of the presence of a patent ductus arteriosus. In no case was a ductus found. In all there was a thrill over the pulmonary artery near its origin. One patient had increased pulmonary flow in the absence of catheterization evidence of a left-to-right intracardiac shunt. In addition, at operation traction on a hemostat which was slipped between the pulmonary artery and aorta while pressure was made on the pulmonary artery anteriorly obliterated the thrill. Another patient also had increased pulmonary flow with no definite evidence of an intracardiac shunt. The levoangiocardiogram demonstrated reopacification of the pulmonary artery with filling of the aorta. There is little doubt of the diagnosis in these two cases. The remaining two were diagnosed on the basis of the thrill found at operation. In one, a thrill was localized over the proximal portion of the aorta and pulmonary artery. In the other the thrill was found to be maximal over the base of the heart and to diminish in intensity as the distal pulmonary artery was reached.

Spencer and Dworkin[4] reported an 18-year-old man in whom a diagnosis of congenital heart disease, possibly patent ductus arteriosus, or possible chronic rheumatic heart disease had been made. At autopsy he was found to have a 2 cm. defect in the aortic septum, with no other malformation.

King and associates[5] made the diagnosis of aortic septal defect in an 11-year-old boy whose physical findings were compatible with the presence of a patent ductus. Cardiac catheterization showed no evidence of an intracardiac shunt, mild pulmonary stenosis, and increased oxygen content of pulmonary artery blood. Angiocardiography revealed a somewhat dilated pulmonary artery. The structures distal to the bifurcation were not well opacified. At operation a thrill

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was discovered in and around the pulmonary artery. No ductus was found. Pressure on the ascending aorta did not obliterate the thrill. It was believed that there existed a defect between the vessels close to the heart.

The patient of Myers et al[6] showed evidence by catheterization of a large left-to-right shunt at the level of the pulmonary artery and pulmonary hypertension. At operation evidence of an aortic septal defect was found.

The patient of Gasul, Fell and Casas[7] was a 3½-months-old infant with a continuous murmur in the pulmonic area. Angiocardiography showed reopacification of the pulmonary artery after filling of the aorta. Thoracic aortography showed the radiopaque substance entering the pulmonary artery from the aorta just above the semilunar valve. There was no evidence of a patent ductus arteriosus.

A series of five patients in whom the diagnosis of aortic septal defect was made by cardiac catheterization were reported by Adams, Diehl, Jorgens and Veasy.[8] One patient died and the diagnosis was confirmed at autopsy. In another the catheter passed through the defect into the aorta. The remaining three cases showed a left-to-right shunt at the level of the pulmonary artery and other findings not typical of a patent ductus.

Dammann[9] described a patient who was operated upon for closure of a patent ductus (atypical murmur) and found to have an aortic septal defect.

Gross[10] recently reported a child who was operated upon for closure of a patent ductus and found to have an aortic septal defect which was successfully closed. Scott and Sabiston[11] reported one case which was also treated successfully by surgery.

We are reporting another example of this malformation because of the somewhat unusual clinical findings and cardiac catheterization data, because of the pulmonary pathology found at autopsy, and because an attempt was made to close the defect.

CASE REPORT

A 12-year-old white boy was noted to have an enlarged heart at birth. At the age of 6 months he was taken to a physician because his heart sounds were thought by his mother to be unusually loud. A diagnosis of cyanotic congenital heart disease was made. At no time during his life, however, were the parents aware of blueness of the lips or nailbeds. He grew normally and his general health was good except for three episodes of pneumonia during the second and third years. He was able to play actively and to engage in all sports. The only limitation he would admit was that during foot races he would become short of breath more quickly than the other boys. He perspired profusely.

On physical examination he was found to have no cyanosis. His development and state of nutrition were normal. There were small pulsations of the carotid arteries. The bony thorax was normal except for a slight depression of the midsternum. The lungs were clear. The heart was enlarged to the left on percussion, and the point of maximum impulse was in the 6th left intercostal space just outside the anterior axillary line. There was no thrill. The cardiac rate was 106 per minute and the rhythm was normal. The pulmonic second sound was accentuated 1 plus. The mitral first sound was loud and sharp. At the apex was heard a high-pitched systolic murmur and a faint presystolic murmur. In the third left intercostal space near the sternal border there was a long, loud, harsh systolic murmur which was transmitted to the neck vessels and posteriorly. The liver was not enlarged. Femoral pulsations were normal. Blood pressure in the right arm was 132/70 mm. Hg, in the left 120/62 mm. Hg, in the legs 110/60 mm. Hg.

Laboratory Data.—The erythrocytes numbered 4.5 million per c. mm., with 13.6 Gm. of hemoglobin. The electrocardiogram showed the P-R interval to be 0.18 second. The QRS was 0.09 second. There was a sinus rhythm and right ventricular strain. Fluoroscopy showed the vascular markings in the mesial thirds of the lung fields to be increased. Peripherally the vessels appeared normal. The pulmonary artery was prominent and pulsated rather vigorously. The heart was moderately enlarged and the apex elevated and blunted. There was no cardiac shadow to the right of the spine. In the right anterior oblique view the right ventricle encroached somewhat on the retrosternal space. In the left anterior oblique view the left ventricle was seen to be enlarged. The left atrium indented the barium-filled esophagus. The aortic shadow was narrowed and pulsated vigorously. No notching of the ribs was noted. The data secured by cardiac catheterization is found in the Table I.

TABLE I. DATA SECURED BY CARDIAC CATHETERIZATION

SITE	PRESSURE (mm. Hg)	OXYGEN CONTENT (VOL. %)
SVC		12.9
IVC		14.6
RA (HIGH)		12.4
RA (MID)	(2)*	12.9
RV (TRICUSPID)		12.2
RV (MID)		12.0
RV (SUBVALVULAR)	120–130 / 0–5 (70)	15.3
PA	120–130 / 70 (95)	15.6
BRACHIAL ARTERY	110–120 / 50–60 (75)	17.8
		Capacity 18.7
		Saturation 95.3

Systemic blood flow 3 L./min.
Pulmonary blood flow 6.9 L./min.
Effective pulmonary blood flow 3 L./min.
Left-to-right shunt 3.9 L./min.

*Figures in parentheses indicate mean pressure.
SVC = Superior vena cava.
IVC = Inferior vena cava.
RA = Right atrium.
RV = Right ventricle.
PA = Pulmonary artery.

Hospital Course.—From a consideration of the clinical, roentgen and electrocardiographic evidence a number of diagnostic possibilities were considered. Most prominent among these was the presence of a high interventricular septal defect. The presence of coarctation of the aorta as an associated anomaly was believed definite. Cardiac catheterization seemed to confirm the presence of a ventricular septal defect. There was pulmonary and right ventricular hypertension of the same magnitude as systemic pressure and a significant difference in oxygen content of blood in the right ventricular outflow region and that in the lower ventricle and right atrium. There was a calculated left-to-right shunt of 3.9 liters per minute.

The degree of hypertension in the right side of the heart was so great that it was felt that the child's outlook was very poor. Although compensation was being maintained it seemed that this state of affairs would probably be of relatively short duration. Operation for closure of the defect by a technique similar to that used for the correction of mitral regurgitation[12] was decided upon.

Using endotracheal oxygen, intravenous Pentothal Sodium and procaine, the thorax was entered through an incision in the third left intercostal space. The ribs were widely spread and the pericardium was incised just anterior and parallel to the left phrenic nerve. When the heart was exposed it was found to be greatly enlarged. Both ventricles appeared to contribute to the enlargement but particularly the right. The most striking finding was an enormous vascular trunk, arising from the heart in the usual position of the great vessels (Fig. 1). A short distance above its origin it divided into two branches. The right branch gave off vessels to the head and upper extremities and the left divided into two vessels, one going to each lung. Careful examination disclosed that the portion of the trunk which became aorta arose posteriorly and was continuous with the left ventricle while the portion which became the pulmonary artery arose anteriorly and was continuous with the right ventricle. There was no perceptible thrill over the huge vessel or its branches but there was a definite diastolic thrill over the right ventricle immediately below the pulmonary valve area. The great trunk was about 3.75 cm. in depth and 6.25 cm. in width. It was apparent that we were dealing with an aortic septal defect of large size.

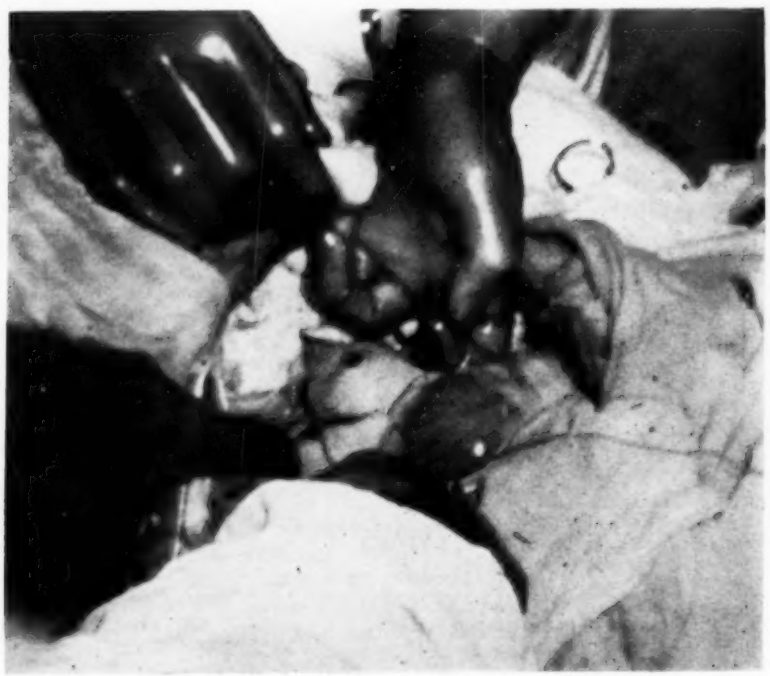

Fig. 1.—The heart and the great vascular trunk as seen at the time of operation.

It was felt that it would be possible to divide the common trunk by sutures and thus obliterate the intercommunication. This was then accomplished. The patient was turned into the left lateral position and the incision extended below the angle of the scapula and around posteriorly. The area of the conjoint vessel was exposed more thoroughly and suturing was begun. Difficulty was encountered in placing the sutures because of the great depth of the vessel. Straight needles with No. 0 silk became practically lost within the lumen; it was not found practical to return the same suture from the posterior aspect to the anterior for tying. Therefore, six separate sutures were placed, and each adjacent pair was tied together posteriorly. Then the anterior ties were made practically simultaneously by the operator and assistants, bringing the anterior and posterior walls together in a vertical fashion and thus dividing the trunk into two vessels. Immediately the patient's heart slowed and the contractions became quite weak. Cyanosis appeared and the blood pressure could not be determined. It was felt that the child might need time to become adjusted to the new situation and for that reason the sutures were not released. A certain

amount of blood had been lost during placement of the sutures and it was thought that this might be responsible, in part, for the depressed state. In spite of our aversion to its use, 500 c.c. of blood were given fairly rapidly. Gradually the tone of the heart improved and contractions became stronger and occurred more rapidly. Because the communication had probably not been completely obliterated, additional mattress sutures of No. 00 braided silk were placed in the region of the adjacent walls without difficulty. The bleeding from the posterior stitch holes was followed by a period of circulatory depression which was corrected by administration of a small amount of blood and of Vasoxyl. The blood pressure rose to 80 mm. Hg systolic and was maintained at that level throughout the rest of the procedure without recourse to any further transfusion or vasopressive drug.

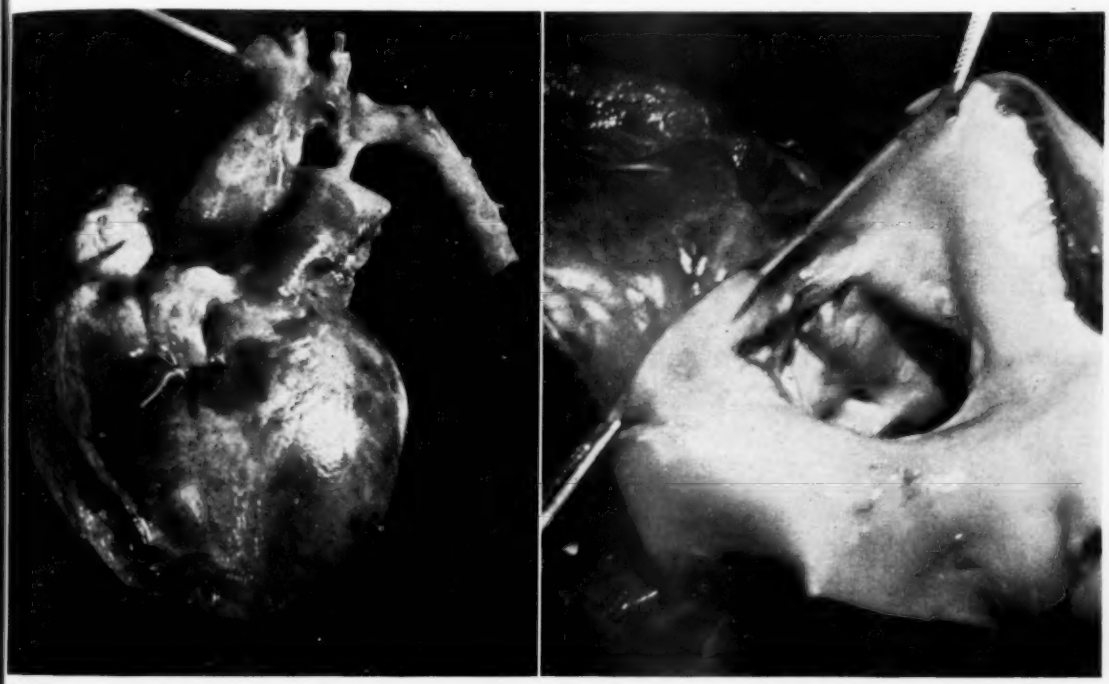

Fig. 2. Fig. 3.

Fig. 2.—The heart seen at autopsy. The vascular trunk appears as it did following the attempted closure of the defect. The incision in the RV outflow track was the avenue of post-mortem exploration.

Fig. 3.—The defect from the pulmonary artery aspect. Atherosclerotic plaques are seen.

For a period of approximately two hours after closure of the chest the child's condition was fairly satisfactory, although cyanosis persisted and he did not respond to painful stimulus. The blood pressure then began to fall and the cyanosis to deepen. It was deemed imperative to re-enter the chest. The original incision was reopened and the pericardial sutures severed. A fair amount of clotted blood was found in the sac. Removal of the blood was not followed by improvement in cardiac action. Rather, the heart slowed and became irregular and weak in its contractions. After a few moments the proximal sutures in the conjoint vessel were removed and the shunt re-established. This was followed by progressive deterioration of cardiac action. Gentle alternate compression and release of the heart was instituted in an attempt to strengthen the tendency to contraction but there was no response. The point of complete asystole was reached and vigorous massage, intracardiac adrenalin and clamping of the aorta were to no avail. The heart lay dilated and flabby and further attempts at resuscitation were abandoned.

The initial step in the post-mortem examination of the heart was the replacement of the sutures in the common trunk. Exploration of the area of closure with finger and probe through a

small incision in the outflow tract of the right ventricle revealed that the lower portion of the suture line had been slightly misplaced. Instead of effectively closing off the inferior aspect of the defect, a channel remained which allowed a shunt from pulmonary artery to aorta; in effect a condition of aortic overriding of the pulmonary valve had been produced.

Routine examination of the heart was then completed. The aorta and pulmonary artery followed their normal course after branching from the common trunk. At the point of insertion of the ligamentum arteriosus, the aorta was constricted, measuring 2 cm. in circumference, while proximally it measured 4.5 cm. and distally 3.5 cm. (Fig. 2). On opening the great vessels, it was seen that at the level of the common trunk there was a defect in the septum between the aorta and pulmonary artery which was 3 cm. in diameter. Its inferior margin was just above the level of the aortic and pulmonary valves and the edge was smooth (Fig. 3). The intima of the pulmonary artery and aorta contained numerous yellow plaques measuring 2 mm. to 1 cm. in size. Both ventricles were hypertrophied and dilated, the walls measuring 1.0 cm. in thickness. The septa were intact. The mitral and tricuspid valves were somewhat thickened along the line of closure.

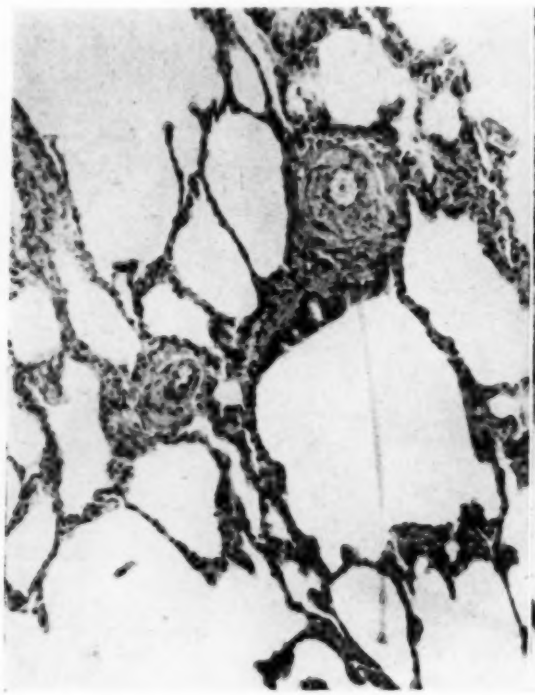

Fig. 4.

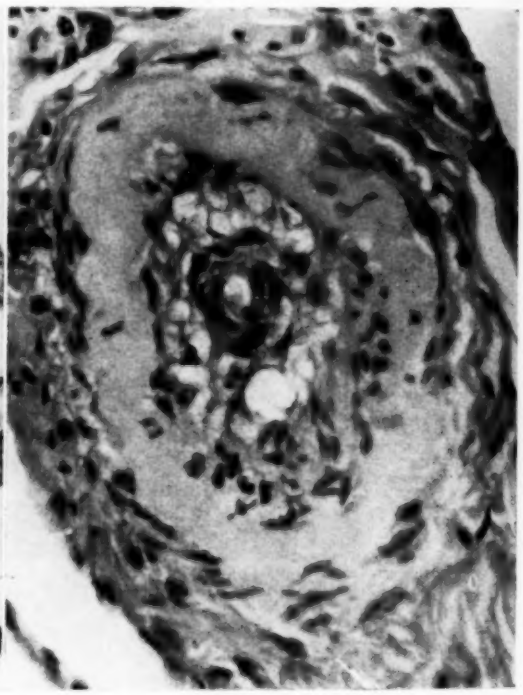

Fig. 5.

Fig. 4.—Two small bronchial arteries. The walls are thickened by medial hypertrophy and the lumen reduced in size.

Fig. 5.—Pulmonary arteriole. Marked thickening of wall and narrowing of lumen.

The right lung weighed 200 grams, the left 110 grams. On section, all lobes were congested. The right and left pulmonary arteries and all branches which could be reached by gross dissection showed yellow plaques on the intimal surface.

Microscopic examination of the heart showed hypertrophy of the myocardial fibers. There was thickening of the free edge of the mitral valve, with edema of the connective tissue and a large number of proliferating fiberblasts. Sections through the edge of the aortic septal defect showed no abnomalities.

The left lung showed atelectasis. Both lungs showed evidence of emphysema, broken alveolar walls and dilated alveoli. Advanced arteriosclerosis was seen in all arteries, from main pulmonary artery to arterioles. The larger arteries showed mainly intimal deposits of lipoid laden macrophages surrounded by myxomatous degenerative changes and lymphocytes. The smaller arteries and arterioles showed medial hypertrophy and intimal hyperplasia. In some of the small arteries the changes consisted of large subintimal vacuoles. These changes tended to narrow the lumen of the vessel and in some instances almost obliterated it (Figs. 4 to 7).

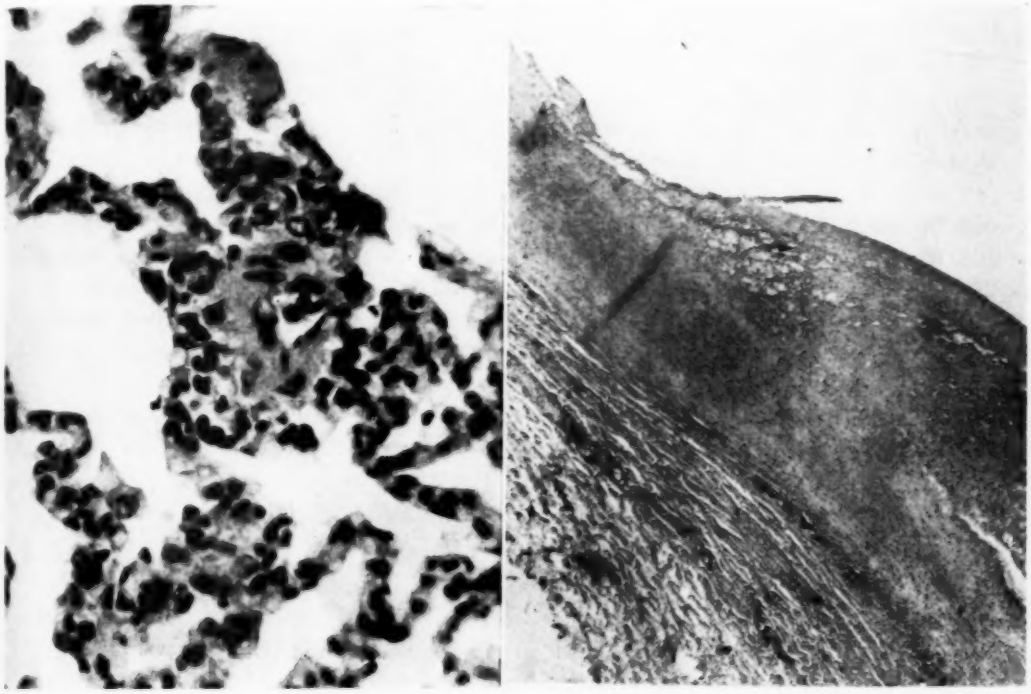

Fig. 6. Fig. 7.

Fig. 6.—Medium sized artery. Lumen is extremely narrowed by intimal hyperplasia, subintimal vacuolization and medial hypertrophy.

Fig. 7.—Pulmonary artery wall. Atheroma of intima.

COMMENT

The criteria upon which the diagnosis of high interventricular septal defect was based seemed to be adequate. We have obtained similar data in other cases later proved. It is obvious, however, that the increased oxygen content of the blood in the outflow tract of the right ventricle was due to regurgitation of mixed blood from the pulmonary artery and not to a shunt at the ventricular level.

The events following closure of the defect require consideration. The cyanosis which developed was thought at the time of its appearance to be due to a right-to-left shunt, it being postulated that another defect, of obscure nature, was present which in some manner was allowed to function after the aortic septal defect had been closed. The discovery at post-mortem examination that the aorta actually overrode the pulmonary valve furnished the explanation, one which should have been obvious. The drop in systemic pressure, peripheral pulmonary

resistance and the new anatomic relationship all contributed to the right-to-left shunt. Had the region of the defect been explored at the time of its closure, the mechanism of the shunt would have been discovered and the suture line revised. This exploration will certainly be conducted in future cases.

The operation itself seems feasible for defects of the type encountered here. For smaller defects, the use of Potts ductus clamps might facilitate suturing. Gross' patient[10] was fortunate in that she had a small communication which allowed passage of a tape ligature around it. When this was tied down the communication was entirely interrupted. Gross points out that this technique is applicable only in selected cases. Scott and Sabiston[11] succeeded in closing an aortic-pulmonary artery communication by clamping the region between the two vessels and suturing the walls together.

The death of the present patient was no doubt due to two main factors: diminished cardiopulmonary reserve and the anoxia produced by the acute right-to-left shunt. Victims of this malformation (at least those patients with evidence of advanced effects on the circulatory apparatus) apparently do not tolerate operation well. The patient previously reported from this institution[1] died on the table shortly after thoracotomy. One patient of Adams and associates[8] died while the defect was being closed. This would indicate that early operation is indicated. If delayed, cardiac reserve may be so diminished that even a successful closure will not benefit the patient.

PULMONARY CHANGES

The changes in the pulmonary artery system of this patient were striking. Atherosclerotic plaques, medial hypertrophy and intimal hyperplasia were widespread. The medial and intimal changes resulted in narrowing of the lumina of the vessels, with consequent increase in resistance to pulmonary flow. Similar changes are found in other conditions in which there is a large left-to-right shunt, such as patent ductus arteriosus, high ventricular septal defect (Eisenmenger complex), atrial septal defect. The cause of this pathologic feature is not clear. The increased flow in itself is the most obvious factor. The fact that the blood has a higher content of oxygen than normal pulmonary artery blood may be important. Edwards[13] explains the changes in Eisenmenger's complex and other malformations as a protective response. By increasing pulmonary resistance there is ultimately a decrease in the shunt and a greater systemic flow.

DISCUSSION

The diagnosis of aortic septal defect remains a problem. Clinical, routine roentgen and electrocardiographic data are not sufficient. Cardiac catheterization does not appear adequate. If the catheter passes through the defect and one is certain that it courses anteriorly and has not entered the aorta via a ventricular septal defect, the evidence is conclusive. However, proving the existence of a left-to-right shunt into the pulmonary artery in a patient whose murmur is not typical of that of patent ductus arteriosus is not diagnostic. There are many patent ducti which produce atypical murmurs and in a number of cases of aortic septal defect the murmur has simulated that of a ductus. A diagnosis made at

exploratory operation should, we feel, be based on firmer ground than the mere presence of a thrill over the pulmonary artery in the absence of a ductus. We base this assertion on our recent experience with two patients who were explored because of the possibility of a patent ductus with atypical signs. In each, cardiac catheterization was productive of inconclusive data. The first child was found to have a ligamentum arteriosus. There was a prominent thrill over the origin of the dilated pulmonary artery and the base of the aorta. The presence of an aortic septal defect was suspected and the pulmonary artery explored. A purse-string ligature was placed in the myocardium of the right ventricular outflow tract and a small incision made within its confines. An exploratory probe was inserted and advanced into the pulmonary artery. Thorough search was made for a communication into the aorta but none was found. A ventricular septal defect was sought, but without success. The second patient had no ductus. A prominent thrill was present over the dilated pulmonary artery from its origin. A purse-string ligature was placed in the wall of the pulmonary artery and exploration of the vessel carried out. No communication with the aorta could be demonstrated. In spite of the lack of definite catheterization evidence of an intracardiac shunt and, in the first case, of failure to palpate it with a probe, we feel that both patients probably had a small defect high in the ventricular septum.

King and associates[3] mention an angiocardiographic finding which they believe may be of aid in diagnosis in some cases. This consists of failure to visualize well the pulmonary artery branches distal to the bifurcation because of the dilution of the radiopaque substance by the large amount of blood shunted from the aorta. They point out that this is less likely to occur with the usual patent ductus, possibly because the shunt is ordinarily smaller than in aortic septal defect. This finding is merely suggestive, at best. The usual ductus may cause a shunt equal to that of a small aortic septal defect and a large ductus may cause a greater shunt than a large aortic septal defect.

Thoracic aortography, as pointed out in the earlier communication[1] and as confirmed by Gasul and associates[7] is the diagnostic method of choice. When the radiopaque substance is injected directly into the base of the ascending aorta it is seen to opacify immediately the pulmonary artery before opacification of the arch of the aorta. Retrograde injection of the substance may not be satisfactory. Unless the shunt is directly visualized, one does not know whether pulmonary artery opacification is via a patent ductus or an aortic septal defect since the whole arch is opacified.

The patients to be subjected to aortography to rule in or out an aortic septal defect include those whose routine roentgen and catheterization findings are consistent with the presence of an aortic-pulmonary shunt and whose clinical findings are not typical of a patent ductus.

SUMMARY

The recent literature on aortic septal defect is reviewed.

A patient is reported whose clinical, roentgen, and cardiac catheterization findings were indicative of a high ventricular septal defect. At operation the subject was found to have an aortic septal defect. Surgical closure was attempted but the patient expired.

At autopsy, in addition to the aortic septal defect, there were found marked changes in the pulmonary arterial system.

Thoracic aortography is at present the method of choice for preoperative diagnosis.

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Book Reviews

RHEUMATIC FEVER, A SYMPOSIUM. Edited by Lewis Thomas. Minneapolis, 1952, University of Minnesota Press. Price $10.00.

This symposium consists of twenty-three papers originally given at a conference at the University of Minnesota on Nov. 29, 30, and Dec. 1, 1951 under the sponsorship of the Minnesota Heart Association. It was indeed a "high level" conference. The names of the participants are well known to those who have followed research in rheumatic fever and rheumatic heart disease during recent years. The problem is surveyed from the standpoint of the natural history of rheumatic fever, the epidemiology, pathology, and the role of the hemolytic streptococcus as an etiological agent. There is also discussion of the biochemical and serologic aspects of the disease and finally the treatment and prevention of rheumatic fever. The articles on prevention and treatment of this disease will prove of special interest to the clinician. The clinician may also be surprised to note that not a single paper is devoted to a discussion of diagnosis. This offers mute testimony to the fact that the diagnosis continues to rest on empirical grounds and that research in this field must continue. The book offers an admirable summary of our present knowledge of rheumatic fever, and points the way towards further experimentation.

S.G.

ANEURYSMS, the Latin text of Rome, 1745, Giovanni Maria Lancisi, 1654-1720. Revised with translation and notes by Wilmer Cave Wright. New York, 1952, The Macmillan Company, 362 pages. $7.50.

Sponsored by the New York Academy of Medicine as number 10 of its useful History of Medicine series, this scholarly edition and translation of the classic work on the subject can be recommended to the general clinician and pathologist as well as to the heart specialist. The work was first published eight years after Lancisi's death and as part two, preceded by a much less novel treatise on the motion of the heart, a popular title before and after Harvey. Part one is not included in this translation, but there is much on aneurysm of the heart, usually meaning dilatation, which term was preferred by his great pupil Morgagni who used both indiscriminately. The work is distinguished by scientifically recorded case histories and autopsy reports. Lancisi was one of the first to recognize definitely a relationship between syphilis and arterial disease; cases with a positive history he called aneurysma Gallicum! The translation is all that could be desired, as one would expect from Mrs. Wright's scholarly renderings of two other classics, Fracastorius on contagium vivum and Ramazzini on occupational diseases. A professor of Greek, she was not of the medical profession, but certainly deserved well of it; her death last year was a misfortune.

W.W.F.

ELECKTOPHYSIOLOGIE DES HERZENS, DARSTELLUNG, KRITIK, PROBLEME. By K. E. Rothschuh. Darmstadt, 1952, Dietrich Steinkopff, 447 pages, 7 tables, 145 figures.

The monograph deals with the electrophysiologic basis and the theory of the electrocardiogram. Although the mechanism of the most important electrocardiographic abnormalities is discussed, it is not a textbook of electrocardiography. As an example of its character, out of the 145 illustrations, very few are conventional electrocardiograms. The title is well chosen to convey the content of the book.

As a rule, in textbooks of electrocardiography, the material is grouped according to the main lesions such as ventricular preponderance and myocardial infarction. In this monograph, the discussion is centered on the fundamental variables of excitation in their application to the normal (second part) and abnormal (third part) electrocardiogram. The first part of the book is concerned with the fundamentals of electrophysiology, specifically the membrane theory, in their application to excitation, excitability, impulse formation, conduction, and rhythmicity.

The discussion of the mechanism of the S-T segment deviations may serve as an example for the treatment of the material. The following processes may be involved: (1) Delay of conduction in ischemic parts, producing potential differences between normal and ischemic zones (Weber's "Verspätungs-Theorie"); (2) different shunt conditions for the hypertrophic ventricle, producing potential differences between normal and hypertrophic parts; (3) local decrease of the action potential in damaged fibers; (4) shortening of the duration of excitation (Schellong's "Plateauverlust"); (5) appearance of superimposed monophasic action currents (Schütz's and Rothschuh's "monophasische Beimischung"); and (6) injury potentials. The pro and con of the various mechanisms and hypotheses in the application to various conditions is critically discussed on the basis of comprehensive examination of the literature. That this discussion is biased is not surprising; any author is tempted to favor one or the other theory. For instance, the view, mostly expressed in the German literature, that the S-T depression in ventricular hypertrophy always indicates secondary myocardial damage, is accepted (p. 399), ignoring the indication from ventricular gradient analysis that the S-T depression may be a physiologic consequence of the increase of the QRS area.

In general, the ventricular gradient is treated somewhat as a stepchild, possibly because it is not easily compatible with the "Difference Theory," which the author favors. A major part of the book attempts to prove that the difference theory accounts satisfactorily for all normal as well as all important abnormal electrocardiographic patterns. However, the difficulties for such generalization are enormous. The "Difference Theory," explains the pattern of the electrocardiogram by two superimposed monophasic action currents of opposite polarity, and slightly different phase, arising in two different parts of the heart. It goes back to Marchand (1877), Waller (1888), and Lewis (1916), but is rejected in this earlier and rather primitive form. The author develops the difference theory from experiments on muscle fibers to the more complex situation of the whole heart with direct and indirect leads. Much of the experimental material has been obtained in the author's laboratory and is quite recent. The author arrives at the conclusion that the difference theory is applicable to certain areas of the whole heart very similar to Nahum's concept, to which reference is made. For instance, the right arm electrode is supposed to record the subepicardial surface of parts of the right ventricle and the subendocardial layers of both ventricles, while the left arm electrode records the outer layers of the left ventricle, of the apex, and also parts of the right ventricle.

In his diagram Fig. 68 (p. 184) illustrating the application of the difference theory to normal position variations in the frontal plane, a central pivot of rotation is accepted, while in fact the fixation point is near the base. This question is important in order to decide which parts of the heart are recorded by a given electrode position.

Although some recent work on spatial vectors is mentioned, the apparent contradiction to the difference theory is not explained, and perhaps not noted, since the author states on p. 247: ". . . it may be regarded as proven that the thorax ECG is mainly due to the potential changes of the *heart as a whole* . . . ." It is true that from anatomically opposite points mirror patterns can be recorded with indirect leads, but they are identical in phase and must, therefore, arise in identical structures.

The difference theory, on the basis of two monophasic action currents, can explain diphasic, but not triphasic patterns. Therefore, for the explanation of triphasic patterns, intrusion of remote potentials or the existence of multiple monophasic currents ("mehrfaches Differenzprinzip") are assumed.

While such an assumption is quite feasible and allows the graphical construction of any pattern, it makes the difference theory so vague and flexible that it loses much of its meaning. It is disturbing that other parts of the heart, in addition to the two areas considered, are to be taken into account when the pattern is triphasic but may be conveniently ignored when it is diphasic.

We mentioned already, that the difference theory is not easily compatible with the ventricular gradient. The ventricular gradient is due to a different pathway of depolarization and repolarization. The difference theory assumes that no change of the pathway takes place; since this would involve different areas in different phases of the cycle.

As a whole, the book is very thorough, very well documented, and stimulating, even if one does not agree with the expressed views. For the American reader it is of great interest as a reference source; it presents European experimental material as well as European lines of thought, which differ from the accepted American interpretation in many important respects. This shows, if anything, the fluid state of present electrocardiographic theory.

The book has no parallel in the American electrocardiographic literature, but it has a certain parallel in Schaefer's monograph "Das Elektrokardiogramm" (reviewed AM. HEART J. **43**:157, 1952). While Schaefer's book is to a very large extent based on the results of his own laboratory, Rothschuh's book covers the literature more completely.

E.S.

In 1950 the International Society of Cardiology nominated Frank N. Wilson, as honorary member, the first time such an honor was bestowed. This choice reflected a tacit testimony of cardiologists the world over for the work of this savant who was the genial constructor of modern electrocardiography.

His death which occurred on Sept. 11, 1952, deprives the cardiology world of one of its most eminent pioneers.

The Committee of the International Society of Cardiology in the name of its member Societies extends to Mrs. Frank Wilson its profound sympathy.

The Secretary General of the I.S.C.:
P. W. Duchosal